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NEW COMPOUNDS

FIELD OF THE INVENTION

The present invention relates to new compounds of formula **I**, as a free base or a pharmaceutically acceptable salt thereof, pharmaceutical formulations containing said compounds and to the use of said compounds in therapy. The present invention further relates to a process for the preparation of compounds of formula **I** and to new intermediates used therein.

An object of the invention is to provide compounds of formula **I** for therapeutic use, especially compounds that are useful for the prevention and/or treatment of conditions associated with glycogen synthase kinase-3 (GSK3) in mammals including man. Particularly, compounds of formula **I** exhibiting an affinity for GSK-3.

BACKGROUND OF THE INVENTION

Glycogen synthase kinase 3 (GSK3) is a serine / threonine protein kinase composed of two isoforms (α and β), which are encoded by distinct genes but are highly homologous within the catalytic domain. GSK3 is highly expressed in the central and peripheral nervous system. GSK3 phosphorylates several substrates including tau, ß-catenin, glycogen synthase, pyruvate dehydrogenase and elongation initiation factor 2b (eIF2b). Insulin and growth factors activate protein kinase B, which phosphorylates GSK3 on serine 9 residue and inactivates it.

Alzheimer's Disease (AD) dementias, and taupathies.

AD is characterized by cognitive decline, cholinergic dysfunction and neuronal death, neurofibrillary tangles and senile plaques consisting of amyloid-β deposits. The sequence of these events in AD is unclear, but believed to be related. Glycogen synthase kinase 3β (GSK3β) or Tau (τ) phosphorylating kinase selectively phosphorylates the microtubule

associated protein τ in neurons at sites that are hyperphosphorylated in AD brains. Hyperphosphorylated protein τ has lower affinity for microtubules and accumulates as paired helical filaments, which are the main components that constitute neurofibrillary tangles and neuropil threads in AD brains. This results in depolymerization of microtubules, which leads to dying back of axons and neuritic dystrophy. Neurofibrillary tangles are consistently found in diseases such as AD, amyotrophic lateral sclerosis, parkinsonism-dementia of Gaum, corticobasal degeneration, dementia pugilistica and head trauma, Down's syndrome, postencephalatic parkinsonism, progressive supranuclear palsy, Niemann-Pick's Disease and Pick's Disease. Addition of amyloid-β to primary hippocampal cultures results in hyperphosphorylation of τ and a paired helical filaments-like state via induction of GSK3β activity, followed by disruption of axonal transport and neuronal death (Imahori and Uchida., J. Biochem 121:179-188, 1997). GSK3β preferentially labels neurofibrillary tangles and has been shown to be active in pre-tangle neurons in AD brains. GSK3 protein levels are also increased by 50% in brain tissue from AD patients. Furthermore, GSK3β phosphorylates pyruvate dehydrogenase, a key enzyme in the glycolytic pathway and prevents the conversion of pyruvate to acetyl-Co-A (Hoshi et al., PNAS 93:2719-2723, 1996). Acetyl-Co-A is critical for the synthesis of acetylcholine, a neurotransmitter with cognitive functions. Thus, GSK3β inhibition may have beneficial effects in progression as well as the cognitive deficits associated with Alzheimer's disease and other above-referred to diseases.

Chronic and Acute Neurodegenerative Diseases.

Growth factor mediated activation of the PI3K /Akt pathway has been shown to play a key role in neuronal survival. The activation of this pathway results in GSK3β inhibition. Recent studies (Bhat et. al., PNAS 97:11074-11079 (2000)) indicate that GSK3β activity is increased in cellular and animal models of neurodegeneration such as cerebral ischemia or after growth factor deprivation. For example, the active site phosphorylation was increased in neurons vulnerable to apoptosis, a type of cell death commonly thought to occur in chronic and acute degenerative diseases such as Alzheimer's Disease, Parkinson's Disease, amyotrophic lateral sclerosis, Huntington's Disease and HIV dementia, ischemic stroke and head trauma. Lithium was neuroprotective in inhibiting apoptosis in cells and in the

brain at doses that resulted in the inhibition of GSK3β. Thus GSK3β inhibitors could be useful in attenuating the course of neurodegenerative diseases.

Bipolar Disorders (BD)

Bipolar Disorders are characterised by manic episodes and depressive episodes. Lithium has been used to treat BD based on its mood stabilising effects. The disadvantage of lithium is the narrow therapeutic window and the danger of overdosing that can lead to lithium intoxication. The recent discovery that lithium inhibits GSK3 at therapeutic concentrations has raised the possibility that this enzyme represents a key target of lithium's action in the brain (Stambolic et al., Curr. Biol. 6:1664-1668, 1996; Klein and Melton; PNAS 93:8455-8459, 1996). Inhibition of GSK3β may therefore be of therapeutic relevance in the treatment of BD as well as in AD patients that have affective disorders.

Schizophrenia

GSK3 is involved in signal transduction cascades of multiple cellular processes, particularly during neural development. Kozlovsky et al (Am J Psychiatry 2000 May;157(5):831-3) found that GSK3β levels were 41% lower in the schizophrenic patients than in comparison subjects. This study indicates that schizophrenia involves neurodevelopmental pathology and that abnormal GSK3 regulation could play a role in schizophrenia. Furthermore, reduced β-catenin levels have been reported in patients exhibiting schizophrenia (Cotter et al., Neuroreport 9:1379-1383 (1998)).

Diabetes

Insulin stimulates glycogen synthesis in skeletal muscles via the dephosphorylation and thus activation of glycogen synthase. Under resting conditions, GSK3 phosphorylates and inactivates glycogen synthase via dephosphorylation. GSK3 is also over-expressed in muscles from Type II diabetic patients (Nikoulina et al., Diabetes 2000 Feb;49(2):263-71). Inhibition of GSK3 increases the activity of glycogen synthase thereby decreasing glucose levels by its conversion to glycogen. GSK3 inhibition may therefore be of therapeutic relevance in the treatment of Type I and Type II diabetes and diabetic neuropathy.

Hair Loss

GSK3 phosphorylates and degrades β-catenin. β-catenin is an effector of the pathway for keratonin synthesis. β-catenin stabilisation may be lead to increase hair development. Mice expressing a stabilised β-catenin by mutation of sites phosphorylated by GSK3 undergo a process resembling de novo hair morphogenesis (Gat et al., Cell 1998 Nov 25;95 (5):605-14)). The new follicles formed sebaceous glands and dermal papilla, normally established only in embryogenesis. Thus GSK3 inhibition may offer treatment for baldness.

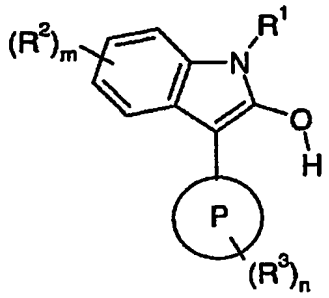
Oral contraceptives

Vijajaraghavan et al. (Biol Reprod 2000 Jun; 62 (6):1647-54) reported that GSK3 is high in motile versus immotile sperm. Immunocytochemistry revealed that GSK3 is present in the flagellum and the anterior portion of the sperm head. These data suggest that GSK3 could be a key element underlying motility initiation in the epididymis and regulation of mature sperm function. Inhibitors of GSK3 could be useful as contraceptives for males.

DISCLOSURE OF THE INVENTION.

The object of the present invention is to provide compounds having an inhibiting effect on GSK3 as well as having a good bioavailability.

Accordingly, the present invention provides a compound of formula I:



(I)

wherein:

P is a 5 or 6-membered heteroaromatic ring containing one or more heteroatoms selected independently from N, O and S of which at least one atom is selected from nitrogen;

R^1 is hydrogen;

R^2 and R^3 are independently selected from halogen, nitro, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{0-6}alkylC_{3-6}cycloalkyl, C_{0-6}alkylaryl, C_{0-6}alkylheteroaryl, CHO, C_{0-6}alkylOR^4, OC_{1-6}alkylOR^4, C_{1-6}alkylSR^4, OC_{1-6}alkylSR^4, $(CO)R^4$, $(CO)OR^4$, $O(CO)R^4$, fluoromethyl, difluoromethyl, trifluoromethyl, fluoromethoxy, difluoromethoxy, trifluoromethoxy, OC_{1-6}alkylcyano, C_{0-6}alkylcyano, C_{0-6}alkylCO_2R^4, OC_{1-6}alkylCO_2R^4, $O(CO)OR^4$, OC_{1-6}alkylCOR^4, C_{1-6}alkylCOR^4, NR^4OR^5, C_{0-6}alkylNR^4R^5, OC_{1-6}alkylNR^4R^5, C_{0-6}alkyl$CONR^4R^5$, OC_{1-6}alkyl$CONR^4R^5$, OC_{1-6}alkyl$NR^4(CO)R^5$, C_{0-6}alkyl$NR^4(CO)R^5$, C_{0-6}alkyl$NR^4(CO)NR^4R^5$, $O(CO)NR^4R^5$, $NR^4(CO)OR^5$, C_{0-6}alkyl$(SO_2)NR^4R^5$, OC_{1-6}alkyl$(SO_2)NR^4R^5$, C_{0-6}alkyl$NR^4(SO_2)R^5$, OC_{1-6}alkyl$NR^4(SO_2)R^5$, C_{0-6}alkyl$(SO)NR^4R^5$, OC_{1-6}alkyl$(SO)NR^4R^5$, SO_3R^4, C_{1-6}alkyl$NR^4(SO_2)NR^4R^5$, C_{0-6}alkyl$NR^4(SO)R^5$, OC_{0-6}alkyl$NR^4(SO)R^5$, OC_{0-6}alkylSO_2R^4, C_{0-6}alkylSO_2R^4, C_{0-6}alkylSOR^4, OC_{1-6}alkylSOR^4 and a group R^6X^1,

wherein X^1 is a direct bond, O, $CONR^7R^8$, $SO_2NR^9R^{10}$, SO_2R^{11} or $NR^{12}R^{13}$;

R^7, R^9 and R^{12} each independently are hydrogen or C_{1-6}alkyl;

R^8, R^{10}, R^{11} and R^{13} are C_{0-4}alkyl;

R^6 is phenyl or a 5, 6 or 7-membered heterocyclic group containing one or two heteroatoms, selected independently from N, O and S, which heterocyclic group may be saturated or unsaturated or said phenyl or 5, 6 or 7-membered heterocyclic group may optionally be fused with a 5 or 6-membered saturated or unsaturated ring containing atoms selected independently from C, N, O and S and which phenyl or heterocyclic group may be substituted with one or two substituents selected from W;

R^6 is linked to R^8, R^{10}, R^{11} and R^{13};

m is 0, 1, 2, 3 or 4;

n is 0, 1, 2, 3 or 4;

R^4 is independently selected from hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{0-6}alkylC_{3-6}cycloalkyl, C_{0-6}alkylaryl, C_{0-6}alkylheteroaryl, C_{1-6}alkyl$NR^{14}R^{15}$ and a 5 or 6 membered heterocyclic group containing one or two heteroatoms, selected independently

from N, O and S, wherein said heterocyclic group may optionally be substituted by a group Y;

R^5 is independently selected from hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{0-6}alkylC_{3-6}cycloalkyl, C_{0-6}alkylaryl, C_{0-6}alkylheteroaryl and C_{1-6}alkyl$NR^{14}R^{15}$ and wherein R^4 and R^5 may together form a 4, 5, 6 or 7-membered heterocyclic group containing one or more heteroatoms selected independently from N, O and S, wherein said heterocyclic group may optionally be substituted by a group Y;

wherein any C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{0-6}alkylC_{3-6}cycloalkyl, C_{0-6}alkylaryl and C_{0-6}alkylheteroaryl defined under R^2 to R^5 may be substituted by one or more group Z;

R^{14} and R^{15} are independently selected from hydrogen, C_{1-6}alkyl and C_{0-6}alkylC_{3-6}cycloalkyl and wherein R^{14} and R^{15} may together form a 5 or 6-membered heterocyclic group containing one or more heteroatoms selected independently from N, O and S, wherein said heterocyclic group may optionally be substituted by a group Y;

W and Z are independently selected from oxo, halogen, nitro, CN, OR^{16}, C_{1-6}alkyl, C_{0-6}alkylaryl, C_{0-6}alkylC_{3-6}cycloalkyl, fluoromethyl, difluoromethyl, trifluoromethyl, fluoromethoxy, difluoromethoxy, trifluoromethoxy, OC_{1-6}alkyl$NR^{16}R^{17}$, $NR^{16}R^{17}$, $CONR^{16}R^{17}$, $NR^{16}(CO)R^{17}$, $O(CO)C_{1-6}$alkyl, $(CO)OC_{1-6}$alkyl, COR^{16}, $(SO_2)NR^{16}R^{17}$, SO_2R^{16}, SOR^{16}, $(CO)C_{1-6}$alkyl$NR^{16}R^{17}$, $(SO_2)C_{1-6}$alkyl$NR^{16}R^{17}$, phenyl and heteroaryl;

Y is selected from oxo, halogen, nitro, CN, OR^{16}, C_{1-6}alkyl, C_{0-6}alkylaryl, C_{0-6}alkylC_{3-6}cycloalkyl, fluoromethyl, difluoromethyl, trifluoromethyl, fluoromethoxy, difluoromethoxy, trifluoromethoxy, OC_{1-6}alkyl$NR^{16}R^{17}$, $NR^{16}R^{17}$, $CONR^{16}R^{17}$, $NR^{16}(CO)R^{17}$, $O(CO)C_{1-6}$alkyl, $(CO)OC_{1-6}$alkyl, COR^{16}, $(SO_2)NR^{16}R^{17}$, SO_2R^{16}, SOR^{16}, $(CO)C_{1-6}$alkyl$NR^{16}R^{17}$, $(SO_2)C_{1-6}$alkyl$NR^{16}R^{17}$, phenyl and heteroaryl, which phenyl or heteroaryl may optionally be substituted by a group W;

R^{16} and R^{17} are independently selected from hydrogen and C_{1-6}alkyl and wherein R^{16} and R^{17} may together form a 5 or 6-membered heterocyclic group containing one or more heteroatoms selected independently from N, O and S;

as a free base or a pharmaceutically acceptable salt thereof.

One aspect of the invention relates to compounds of formula **I**, wherein ring P is a 6-membered heteroaromatic ring containing one or two nitrogen atoms.

In another aspect of the invention ring P is pyridine.

In a further aspect of the invention ring P is pyrimidine.

In another aspect of the invention R^2 and R^3 are independently selected from halogen, nitro, C_{1-6}alkyl, fluoromethyl, difluoromethyl, trifluoromethyl, fluoromethoxy, difluoromethoxy, trifluoromethoxy, $OC_{1-6}alkylNR^4R^5$, C_{0-6}alkylcyano, $C_{0-6}alkylCONR^4R^5$, $C_{0-6}alkyl(SO_2)NR^4R^5$, $C_{0-6}alkylNR^4R^5$ and a group R^6X^1, wherein X^1 is a direct bond, O, $CONR^7R^8$, $SO_2NR^9R^{10}$, SO_2R^{11} or $NR^{12}R^{13}$; R^7, R^9 and R^{12} each independently are hydrogen or C_{1-3}alkyl; R^8, R^{10}, R^{11} and R^{13} are C_{0-4}alkyl; R^6 is phenyl or a 5, 6 or 7-membered heterocyclic group containing one or two heteroatoms, selected independently from N, O and S, which heterocyclic group may be saturated or unsaturated or said phenyl or 5, 6 or 7-membered heterocyclic group may optionally be fused with a 5 or 6-membered saturated or unsaturated ring containing atoms selected independently from C, N, O and S and which phenyl or heterocyclic group may be subtituted with one or two substituents selected from W; and R^6 is linked to R^8, R^{10}, R^{11} and R^{13}.

In another aspect of the invention R^2 and R^3 are independently selected from nitro, C_{1-3}alkyl, C_{0-3}alkylcyano, $C_{0-3}alkylNR^4R^5$, $OC_{1-3}alkylNR^4R^5$, $C_{0-3}alkylCONR^4R^5$ and $C_{0-3}alkyl(SO_2)NR^4R^5$.

In one aspect of the invention R^4 is independently selected from hydrogen, C_{1-6}alkyl and a 5 or 6 membered heterocyclic group containing one or two heteroatoms, selected independently from N, O and S, wherein said heterocyclic group may optionally be substituted by a group Y; R^5 is independently selected from hydrogen, C_{1-6}alkyl and $C_{1-6}alkylNR^{14}R^{15}$ and wherein R^4 and R^5 may together form a 4, 5, 6 or 7-membered heterocyclic group containing one or more heteroatoms selected independently from N and O, wherein said heterocyclic group may optionally be substituted by a group Y; R^{14} and R^{15} are independently selected from hydrogen and C_{1-6}alkyl and wherein

R^{14} and R^{15} may together form a 5 or 6-membered heterocyclic group containing one or more heteroatoms selected independently from N and O, wherein said heterocyclic group may optionally be substituted by a group Y.

Yet another aspect of the invention relates to compounds selected from
2-(5-Cyano-2-hydroxy-1*H*-indol-3-yl)-*N*-[2-(dimethylamino)ethyl]-4-pyridinecarboxamide,
2-Hydroxy-3-[4-[(4-methylpiperazine-1-yl)carbonyl]pyridine-2-yl]-1*H*-indole-5-carbonitrile dihydrochloride,
2-Hydroxy-3-{5-[(4-methylpiperazine-1-yl)carbonyl]pyridine-2-yl}-1*H*-indole-5-carbonitrile,
2-Hydroxy-3-[5-(morpholine-4-ylmethyl)pyridine-2-yl]-1*H*-indole-5-carbonitrile hydrochloride,
2-Hydroxy-3-[6-(2-morpholine-4-ylethoxy)pyrimidine-4-yl]-1*H*-indole-5-carbonitrile,
2-Hydroxy-3-{5-[(4-methylpiperazine-1-yl)methyl]pyridine-2-yl}-1*H*-indole-5-carbonitrile hydrochloride,
2-(5-Cyano-2-hydroxy-1*H*-indol-3-yl)-*N*-[2-(dimethylamino)ethyl]-*N*-methyl-3-pyridinecarboxamide dihydrochloride,
2-Hydroxy-3-[5-(4-methylpiperazine-1-sulfonyl)pyridine-2-yl]-1*H*-indole-5-carbonitrile and
6-(5-Cyano-2-hydroxy-1*H*-indol-3-yl)pyridine-3-sulfonic acid (2-pyrrolidine-1-ylethyl)amide dihydrochloride,
as a free base or a pharmaceutically acceptable salt thereof.

Listed below are definitions of various terms used in the specification and claims to describe the present invention.

For the avoidance of doubt it is to be understood that where in this specification a group is qualified by 'hereinbefore defined', 'defined hereinbefore' or 'defined above' the said group encompasses the first occurring and broadest definition as well as each and all of the other definitions for that group.

For the avoidance of doubt it is to be understood that in this specification 'C_{1-6}' means a carbon group having 1, 2, 3, 4, 5 or 6 carbon atoms.

In this specification, unless stated otherwise, the term "alkyl" includes both straight and branched chain alkyl groups and may be methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, n-pentyl, i-pentyl, t-pentyl, neo-pentyl, n-hexyl or i-hexyl, t-hexyl. The term C_{1-3} alkyl having 1 to 3 carbon atoms and may be methyl, ethyl, n-propyl or i-propyl. The term C_{1-2} alkyl having 1 to 2 carbon atoms and may be methyl or ethyl.

In this specification, unless stated otherwise, the term "cycloalkyl" refers to an optionally substituted, saturated cyclic hydrocarbon ring system. The term "C_{3-6}cycloalkyl" may be cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl.

In this specification, unless stated otherwise, the term "alkylaryl", includes both substituted and unsubstituted alkylaryl groups, which may be substituted on the alkyl and/or the aryl and may be, but are not limited to, C_{1-6}alkylaryl, benzyl or ethylphenyl.

In this specification, unless stated otherwise, the term "alkenyl" includes both straight and branched chain alkenyl groups but references to individual alkenyl groups such as 2-butenyl are specific for the straight chain version only. The term C_2-C_6 alkenyl having 2 to 6 carbon atoms and one or two double bonds, and may be, but is not limited to, vinyl, allyl, propenyl, i-propenyl, butenyl, i-butenyl, crotyl, pentenyl, i-pentenyl or hexenyl.

In this specification, unless stated otherwise, the term "alkynyl" includes both straight and branched chain alkynyl groups but references to individual alkynyl groups such as 2-butynyl are specific for the straight chain version only. The term C_2-C_6 alkynyl having 2 to 6 carbon atoms and one or two trippel bonds, and may be, but is not limited to, etynyl, propargyl, butynyl, i-butynyl, pentynyl, i-pentynyl or hexynyl.

In this specification, unless stated otherwise, the term "5 or 6-membered heteroaromatic ring containing one or more heteroatoms selected independently from N, O and S of which at least one atom is selected from nitrogen" includes, but is not limited to, furyl, isoxazolyl,

isothiazolyl, oxazolyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridyl, pyrimidyl, pyrrolyl, thiazolyl, thienyl, imidazolyl.

In this specification, unless stated otherwise, the terms "5 or 6-membered heterocyclic group containing one or more heteroatoms selected independently from N, O and S" or "5, 6 or 7-membered heterocyclic group containing one or two heteroatoms, selected independently from N, O and S, which heterocyclic group may be saturated or unsaturated" or "4, 5, 6 or 7-membered heterocyclic group containing one or more heteroatoms selected independently from N, O and S" may be, but are not limited to, azepanyl, azitidinyl, imidazolidinyl, imidazolinyl, morpholinyl, piperazinyl, piperidyl, piperidonyl, pyrazolidinyl, pyrazolinyl, pyrrolidinyl, pyrrolinyl, tetrahydropyranyl, thiomorpholinyl, furyl, isoxazolyl, isothiazolyl, oxazolyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridyl, pyrimidyl, pyrrolyl, thiazolyl, thienyl, imidazolyl.

In this specification, unless stated otherwise, the term "5 or 6-membered saturated or unsaturated ring containing atoms selected independently from C, N, O and S", includes both aromatic, heteroaromatic rings and heterocyclic rings that are saturated or unsaturated. Examples of such heterocyclic rings may be, but are not limited to furyl, isoxazolyl, isothiazolyl, oxazolyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridyl, pyrimidyl, pyrrolyl, thiazolyl, thienyl, imidazolyl, imidazolidinyl, imidazolinyl, morpholinyl, piperazinyl, piperidyl, piperidonyl, pyrazolidinyl, pyrazolinyl, pyrrolidinyl, pyrrolinyl, tetrahydropyranyl, thiomorpholinyl, phenyl, cyclohexyl or cyclopentyl.

In this specification, unless stated otherwise, the term "6-membered heteroaromatic ring containing one or two nitrogen atoms" includes, but is not limited to, pyrazinyl, pyrazolyl, pyridazinyl, pyridyl, pyrimidyl or pyrrolyl.

In the case where a subscript is the integer 0 (zero) the group to which the subscript refers to, indicates that the group is absent, i.e. there is a direct bond between the groups.

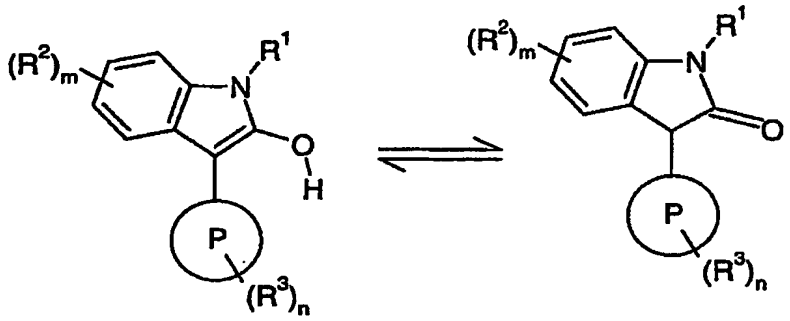
In this specification, unless stated otherwise, the term halogen may be fluorine, chlorine, bromine or iodine.

The present invention relates to the use of compounds of formula I as hereinbefore defined as well as to the salts thereof. Salts for use in pharmaceutical compositions will be pharmaceutically acceptable salts, but other salts may be useful in the production of the compounds of formula I.

Both organic and inorganic acids can be employed to form non-toxic pharmaceutically acceptable salts of the compounds of this invention. Pharmaceutically acceptable salts include, but are not limited to nitrate, hydrochloride, dihydrochloride and acetate. These salts are readily prepared by methods known in the art.

Some compounds of formula I may have chiral centres and/or geometric isomeric centres (E- and Z- isomers), and it is to be understood that the invention encompasses all such optical, diastereoisomeric and geometric isomers.

Within the present invention it is to be understood that a compound of formula I or a salt thereof may exhibit the phenomenon of tautomerism as shown in Figure 1. It is to be understood that the invention encompasses any tautomeric form of compounds of formula I and is not to be limited merely to any one tautomeric form utilized within the formula drawings:



(I) (II)

Figure 1

wherein P, R^1, R^2, R^3, m and n are as defined above.

Pharmaceutical compositions

According to one aspect of the present invention there is provided a pharmaceutical composition comprising a compound of formula **I**, as a free base or a pharmaceutically acceptable salt thereof, for use in the prevention and/or treatment of conditions associated with glycogen synthase kinase-3.

The composition may be in a form suitable for oral administration, for example as a tablet, pill, syrup, powder, granule or capsule, for parenteral injection (including intravenous, subcutaneous, intramuscular, intravascular or infusion) as a sterile solution, suspension or emulsion, for topical administration as an ointment, patch or cream or for rectal administration as a suppository.
In general, the above compositions may be prepared in a conventional manner using pharmaceutically carriers or diluents.

Suitable daily doses of the compounds of formula **I** in the treatment of a mammal, including man, are approximately 0.01 to 250 mg/kg bodyweight at peroral administration and about 0.001 to 250 mg/kg bodyweight at parenteral administration. The typical daily dose of the active ingredients varies within a wide range and will depend on various factors such as the relevant indication, the route of administration, the age, weight and sex of the patient and may be determined by a physician.

Medical use

Surprisingly, it has been found that the compounds defined in the present invention, as a free base or a pharmaceutically acceptable salt thereof, are well suited for inhibiting glycogen synthase kinase-3 (GSK3). Accordingly, the compounds of the present invention are expected to be useful in the prevention and/or treatment of conditions associated with glycogen synthase kinase-3 activity, i.e. the compounds may be used to produce an

inhibitory effect of GSK3 in mammals, including man, in need of such prevention and/or treatment.

GSK3 is highly expressed in the central and peripheral nervous system and in other tissues. Thus, it is expected that compounds of the invention are well suited for the prevention and/or treatment of conditions associated with glycogen synthase kinase-3 in the central and peripheral nervous system. In particular, the compounds of the invention are expected to be suitable for prevention and/or treatment of one or more conditions such as dementia, Alzheimer's Disease, Parkinson's Disease, Frontotemporal dementia Parkinson's Type, Parkinson dementia complex of Gaum, HIV dementia, diseases with associated neurofibrillar tangle pathologies, amyotrophic lateral sclerosis, corticobasal degeneration, dementia pugilistica, Down's syndrome, Huntington's Disease, postencephelatic parkinsonism, progressive supranuclear palsy, Pick's Disease, Niemann-Pick's Disease, stroke, head trauma and other chronic neurodegenerative diseases, Bipolar Disease, affective disorders, depression, schizophrenia, cognitive disorders, Type I and Type II diabetes and diabetic neuropathy, hair loss and contraceptive medication.

The dose required for the therapeutic or preventive treatment of a particular disease will necessarily be varied depending on the host treated, the route of administration and the severity of the illness being treated.

The present invention relates also to the use of a compound of formula I as defined hereinbefore, in the manufacture of a medicament for the prevention and/or treatment of conditions associated with GSK3.

In the context of the present specification, the term "therapy" includes treatment as well as prevention, unless there are specific indications to the contrary. The terms "therapeutic" and "therapeutically" should be construed accordingly.

The invention also provides a method of treatment and/or prevention of conditions associated with GSK3, in a patient suffering from, or at risk of, said condition, which

comprises administering to the patient an effective amount of a compound of formula I, as hereinbefore defined.

Non- Medical use

In addition to their use in therapy, the compounds of formula I, as a free base or a pharmaceutically acceptable salt thereof, are also useful as pharmacological tools in the development and standardisation of *in vitro* and *in vivo* test systems for the evaluation of the effects of inhibitors of GSK3 in laboratory animals such as cats, dogs, rabbits, monkeys, rats and mice, as part of the search for new therapeutical agents.

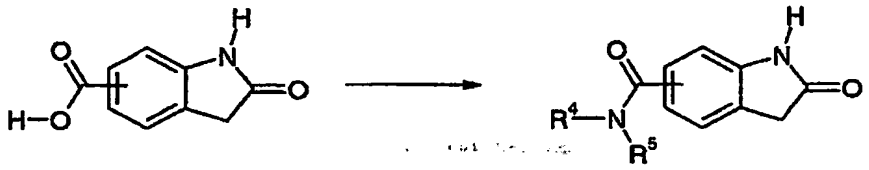
Methods of Preparation

The present invention also relates to processes for preparing the compound of formula I. Throughout the following description of such processes it is understood that, where appropriate, suitable protecting groups will be added to, and subsequently removed from the various reactants and intermediates in a manner that will be readily understood by one skilled in the art of organic synthesis. Conventional procedures for using such protecting groups as well as examples of suitable protecting groups are for example described in "Protective Groups in Organic Synthesis", T.W. Greene, P.G.M Wutz, Wiley-Interscience, New York, 1999.

Preparation of Intermediates

The process, wherein halo is halogen and halogen, R^3, R^4, R^5, n and m, unless otherwise specified, are as defined hereinbefore, and n and m are 0, 1, 2 or 3, comprises,

(i) Conversion of a compound of formula II to a compound of formula III,



(II) (III)

may be carried out by activation of the acid function in a compound of formula II with a) a halogenation reagent such as thionyl chloride or oxalyl chlorid in a suitable solvent such as methylene chloride or toluene or using the reagent neat and the reaction may occur at a temperature between 0 °C and +80 °C followed by,

a reaction with the appropriate substituted amine R^4R^5NH in a suitable solvent such as methylene chloride, chloroform or acetonitrile in the presence of a suitable base such as an alkali metal, an alkaline earth metal carbonate or hydroxide such as sodium carbonate, potassium carbonate, calcium carbonate, sodium hydroxide or potassium hydroxide or an alkyl amine base such as triethylamine and the reaction may occur at a temperature between -20 °C and +80 °C, or

b) a suitable coupling reagent such as 1,1'-carbonyldiimidazole or 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide in a suitable solvent such as *N,N*-dimethylformamide or tetrahydrofurane, the reaction may occur at a temperature between +20 °C and +130 °C followed by addition with the appropriate substituted amine R^4R^5NH at a reaction temperature between +20 °C and +130 °C.

(ii) Conversion of a compound of formula IV to a compound of formula V,

(IV) (V)

may be carried out by

a) a Friedel-Craft acylation using an acylating reagent such as chloroacetyl chloride and aluminum trichloride in a suitable solvent such as methylene chloride, chloroform or nitrobenzene at a reaction temperature between about 0 °C and 60 °C followed by, a reaction of the formed chloroketone with pyridine at a reaction temperature between +20 °C and reflux followed by,

hydrolysis in a suitable solvent such as water or a mixture of water and an alcohol such as ethanol or methanol in the presence of a suitable base such as sodium hydroxide or potassium hydroxide, at a reaction temperature between +20 °C and reflux.

(iii) Conversion of a compound of formula **VI** to a compound of formula **VII**,

(VI) **(VII)**

may be carried out by activation of the acid function in a compound of formula **VI** with

a) a halogenation reagent such as thionyl chloride or oxalyl chlorid in a suitable solvent such as methylene chloride or toluene or using the reagent neat followed by a reaction with the appropriate substituted amine R^4R^5NH in a suitable solvent such as methylene chloride, chloroform or acetonitrile in the presence of a suitable base such as an alkali metal, an alkaline earth metal carbonate or hydroxide such as sodium carbonate, potassium carbonate, calcium carbonate, sodium hydroxide or potassium hydroxide or an alkyl amine base such as triethylamine, the reaction may occur at a temperature between -70 °C and +80 °C, or

b) a suitable coupling reagent such as 1,1'-carbonyldiimidazole or 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide in a suitable solvent such as *N,N*-dimethylformamide

or tetrahydrofurane and the reaction may occur at a temperature between +20 °C and +130 °C, followed by

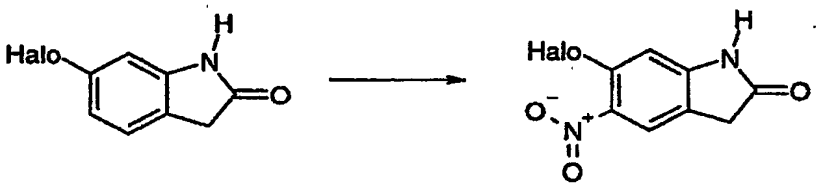
addition with the appropriate substituted amine R^4R^5NH, at a reaction temperature between +20 °C and +130 °C.

(iv) Halogenation of a compound of formula VIII,

(VIII) (IX)

wherein R_2 is C_{1-6}alkyl to obtain a compound of formula IX may be performed by an aromatic electrophilic substitution using a suitable halogenation agent such as Br_2, Cl_2, I_2, ICl, SO_2Cl_2 or another suitable halogenation agent such as *N*-bromosuccinimid in an appropriate solvent such as acetonitrile, acetic acid, HCl/ethanol or water, with or without a suitable base e.g. an alkali metal acetate such as sodium acetate, at a reaction temperature between -20 °C and room temperature.

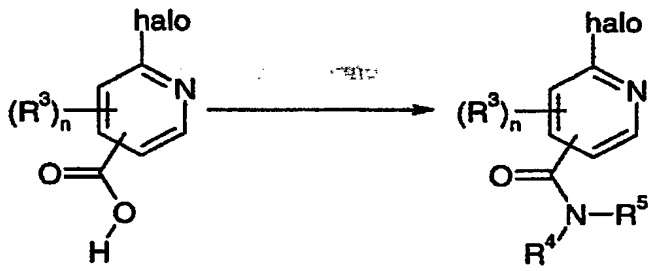
(v) Nitration of a compound of formula IV to obtain a compound of formula X,



(IV) (X)

may be carried out by aromatic electrophilic substitution using a suitable nitration reagent such as potassium nitrate or nitric acid in a suitable solvent such as acetic acid, acetic anhydride, sulphuric acid or water at a reaction temperature between -20 °C and room temperature.

(vi) Conversion of a compound of formula **XI** to a compound of formula **XII** may be carried out by



XI **XII**

activation of the acid function in a compound of formula **XI**, with

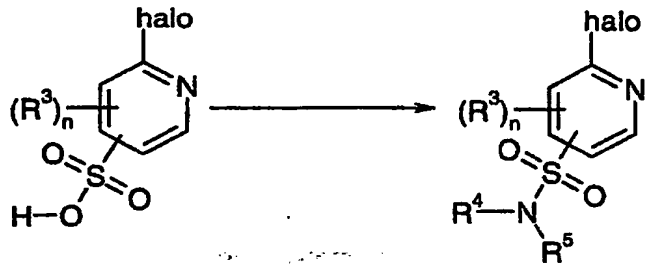
a) a halogenation reagent such as thionyl chloride or oxalyl chlorid in a suitable solvent such as methylene chloride, chloroform or toluene or using the reagent neat and the reaction may occur at a temperature between 0 °C and +80 °C, followed by

a reaction with the appropriate substituted amine R^4R^5NH in a suitable solvent such as methylene chloride, chloroform, toluene or acetonitrile in the presence of a suitable base such as an alkali metal, an alkaline earth metal carbonate or hydroxide such as sodium carbonate, potassium carbonate, calcium carbonate, sodium hydroxide or potassium hydroxide or an alkyl amine base such as triethylamine, the reaction may occur at a temperature between -20 °C and +80 °C, or

b) a suitable coupling reagent such as 1,1'-carbonyldiimidazole or 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide in a suitable solvent such as *N,N*-dimethylformamide or tetrahydrofurane, the reaction may occur at a temperature between +20 °C and +130 °C, followed by

addition with the appropriate substituted amine R^4R^5NH and at a reaction temperature between +20 °C and +130 °C.

(vii) Conversion of a compound of formula **XIII** to a compound of formula **XIV** may be carried out by

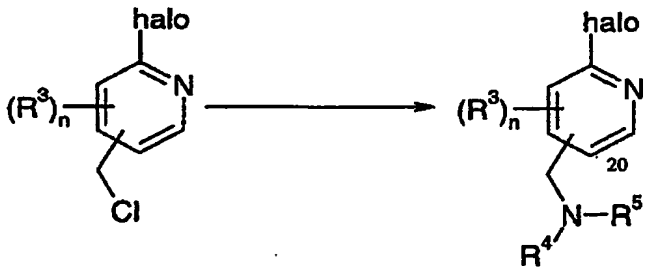


XIII XIV

transfering the sulfonic acid function to the sulfonyl chloride with a suitable halogenating reagent such as thionyl chloride or phosphorus oxychloride in a suitable solvent such as methylene chloride, chloroform, acetonitrile or toluene, and sulfolane may be added as a co-solvent to facilitate the reaction. A catalytic amount of *N,N*-dimethylacetamid may speed up the reaction and the reaction may occur at a temperature between 0 °C and + 120 °C, followed by

the addition of an appropriate amine R^4R^5NH in a suitable solvent such as methylene chloride, chloroform, acetonitrile or toluene and the reaction may occur at a temperature between 0 °C and + 110 °C.

(viii) Reaction of a compound of formula **XV** to a compound of formula **XVI** may be carried out by

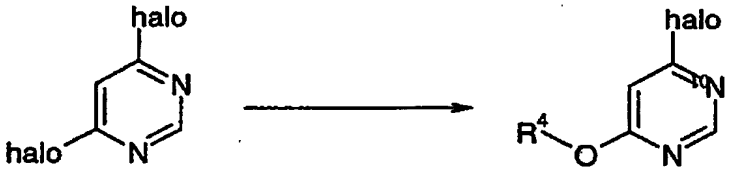


XV XVI

a reaction with an appropriate amine R^4R^5NH in a suitable solvent such as methylene chloride, chloroform, acetonitrile or *N,N*-dimethylformamide with or without a suitable base such as an alkali metal, an alkaline earth metal carbonate or hydroxide such as sodium

carbonate, potassium carbonate, calcium carbonate, sodium hydroxide or potassium hydroxide or an alkyl amine base such as triethylamine, the reaction may occur at a temperature between 0 °C and + 120 °C.

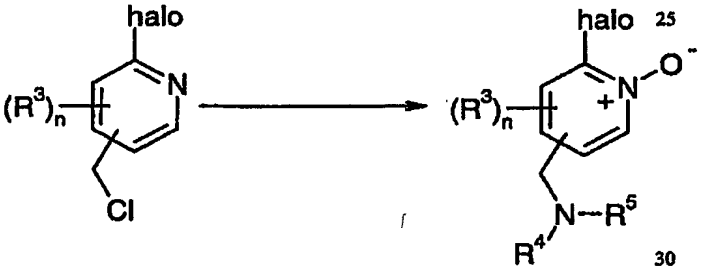
(ix) Reaction of a compound of formula **XVII** to a compound of formula **XVIII** may be carried out by



XVII **XVIII**

a reaction with an appropriate reagent R^4OH in a suitable solvent such as acetonitrile, methylene chloride, chloroform, toluene or *N,N*-dimethylformamide in the presence of a suitable base such as an alkali metal, an alkaline earth metal carbonate, hydroxide or hydride such as sodium carbonate, potassium carbonate, calcium carbonate, sodium hydroxide, potassium hydroxide or sodium hydride or an alkyl amine base such as triethylamine and the reaction may occur at a temperature between 0 °C and +80 °C.

(x) Conversion of a compound of formula **XIX** to a compound of formula **XX** may be carried out by



XIX (XV) **XX**

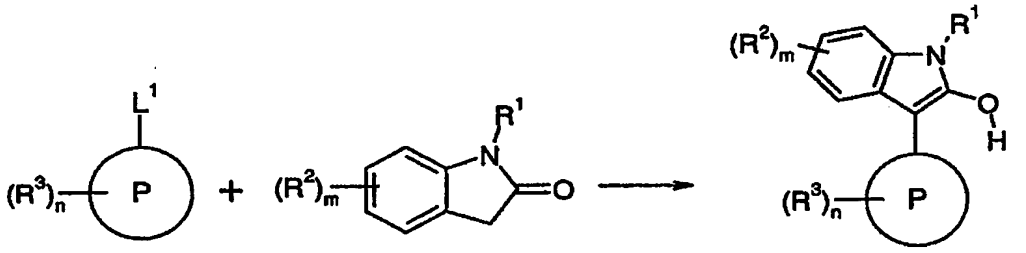
a) oxidation of the ring nitrogen in a compound of formula **XIX**, with the exception when R^3 is a substituent that is susceptible to certain oxidation agents, using a suitable reagent such as 3-chloroperoxybenzoic acid, hydrogen peroxide/peroxytrifluoroacetic acid or hydrogen peroxide urea complex/trifluoroacetic anhydride in a suitable solvent such as methylene chloride, chloroform, toluene, acetonitrile or tetrahydrofuran and the reaction may occur at a temperature between 0 °C and +100 °C, followed by
reacting the formed pyridine *N*-oxide intermediate to a compound of formula **XX** which may be carried out by a reaction with an appropriate amine R^4R^5NH in a suitable solvent such as methylene chloride, chloroform, acetonitrile or *N,N*-dimethylformamide with or without a suitable base such as an alkali metal, an alkaline earth metal carbonate or hydroxide such as sodium carbonate, potassium carbonate, calcium carbonate, sodium hydroxide or potassium hydroxide or an alkyl amine base such as triethylamine and the reaction may occur at a temperature between 0 °C and + 120 °C.

Methods of Preparation of End products

Another object of the invention are processes **a** and **b** for the preparation of a compound of general formula **I**, wherein halo is halogen and halogen, P, R^1, R^2, R^3, R^4, R^5, m and n, unless otherwise specified, are defined as hereinbefore, and salts thereof.

These processes comprise;

a) reacting a compound of formula **B**, wherein L^1 is a leaving group such as halogen, e.g. fluorine, chlorine or bromine, with a compound of formula **C**,



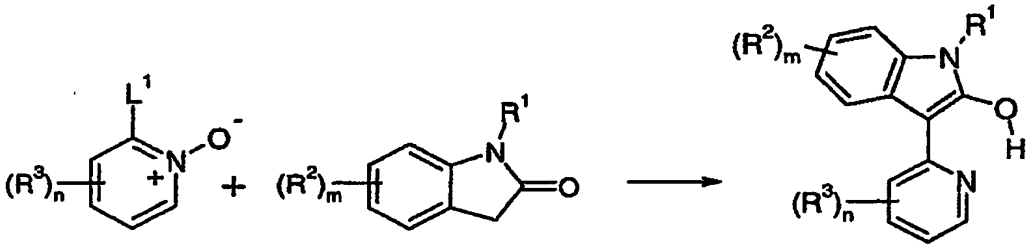
(B (XII, XIV, XVI, XVIII)) **(C (III, V, VII, IX, X))** **(I)**

The reaction of process **a** may be carried out in an appropriate solvent such as an ether e.g. tetrahydrofuran or 1,4-dioxan, an aromatic hydrocarbon solvent such as toluene or a

dipolar aprotic solvent such as *N,N*-dimethylformamide, *N,N*-dimethylacetamide, *N*-methylpyrrolidin-2-one or dimethylsulphoxide and the reaction may occur at a temperature between +10 °C and +150 °C.

The reaction is advantageously effected in the presence of a base. A suitable base may be an organic amine base such as pyridine, 2,6-lutidine, collidine, 4-dimethylaminopyridine, triethylamine, morpholine, *N*-methylmorpholine, diazabicyclo[5.4.0]undec-7-ene, tetramethylguanidine or an alkali metal or an alkaline earth metal carbonate or hydroxide such as sodium carbonate, potassium carbonate, calcium carbonate, sodium hydroxide or potassium hydroxide. Alternatively, such a base may be an alkali metal hydride such as sodium hydride, or an alkali metal or alkaline earth metal amide such as sodium amide, sodium bis(trimethylsilyl)amide, potassium amide or potassium bis(trimethylsilyl)amide. When it is desired to obtain the acid salt, the free base may be treated with an acid such as a hydrogen halide such as hydrogen chloride, sulphuric acid, a sulphonic acid such as methane sulphonic acid or a carboxylic acid such as acetic or citric acid in a suitable solvent such as tetrahydrofuran, diethyl ether, chloroform or methylene chloride or mixtures thereof, the reaction may occur between -30 °C to +50 °C,

b) reacting a compound of formula **D**, wherein L^1 is a leaving group such as halogen, e.g. fluorine, chlorine or bromine, with a compound of formula **C**, followed by removal of the *N*-oxide, to form a compound of formula **I**, wherein P is a pyridine,



(D (XX)) **(C (III, V, VII, IX, X))** **(I)**

The reaction of process **b** may be carried out in an appropriate solvent such as an ether e.g. tetrahydrofuran or 1,4-dioxan, an aromatic hydrocarbon solvent such as toluene, or a dipolar aprotic solvent such as *N,N*-dimethylformamide, *N,N*-dimethylacetamide,

N-methylpyrrolidin-2-one or dimethylsulphoxide, the reaction may occur at a temperature between +10 °C and +150 °C.

The reaction is advantageously effected in the presence of a base. Such a base may be an organic amine base such as pyridine, 2,6-lutidine, collidine, 4-dimethylaminopyridine, triethylamine, morpholine, *N*-methylmorpholine, diazabicyclo[5.4.0]undec-7-ene, tetramethylguanidine or an alkali metal or an alkaline earth metal carbonate or hydroxide such as sodium carbonate, potassium carbonate, calcium carbonate, sodium hydroxide or potassium hydroxide. Alternatively, such a base may be an alkali metal hydride such as sodium hydride, an alkali metal or an alkaline earth metal amide such as sodium amide, sodium bis(trimethylsilyl)amide, potassium amide or potassium bis(trimethylsilyl)amide.

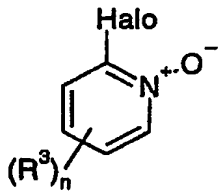
The *N*-oxide may be removed by using a suitable reagent such as phosphorus trichloride in a suitable solvent such as methylene chloride, chloroform, toluene or ethyl acetate and the reaction may occur at a temperature between 0 °C and +100 °C.

When it is desired to obtain the acid salt, the free base may be treated with an acid such as a hydrogen halide such as hydrogen chloride, sulphuric acid, a sulphonic acid such as methane sulphonic acid or a carboxylic acid such as acetic or citric acid in a suitable solvent such as tetrahydrofuran, diethyl ether, chloroform or methylene chloride or mixtures thereof, the reaction may occur between -30 °C to +50 °C.

Intermediates

The present invention further relates to new intermediates and the use of these intermediates in the preparation of compounds of formula I as defined hereinbefore.

In one aspect of the invention the intermediate is a compound of formula **XXI**



(XXI)

wherein:

halo is halogen;

R^3 is selected from halogen, nitro, C_{1-6}alkyl, C_{2-6}alkenyl,

C_{2-6}alkynyl, C_{0-6}alkylC_{3-6}cycloalkyl, C_{0-6}alkylaryl, C_{0-6}alkylheteroaryl, CHO, C_{0-6}alkylOR^4, OC_{1-6}alkylOR^4, C_{1-6}alkylSR^4, OC_{1-6}alkylSR^4, $(CO)R^4$, $(CO)OR^4$, $O(CO)R^4$, fluoromethyl, difluoromethyl, trifluoromethyl, fluoromethoxy, difluoromethoxy, trifluoromethoxy, OC_{1-6}alkylcyano, C_{0-6}alkylcyano, C_{0-6}alkylCO_2R^4, OC_{1-6}alkylCO_2R^4, $O(CO)OR^4$, OC_{1-6}alkylCOR^4, C_{1-6}alkylCOR^4, NR^4OR^5, C_{0-6}alkylNR^4R^5, OC_{1-6}alkylNR^4R^5, C_{0-6}alkyl$CONR^4R^5$, OC_{1-6}alkyl$CONR^4R^5$, OC_{1-6}alkyl$NR^4(CO)R^5$, C_{0-6}alkyl$NR^4(CO)R^5$, C_{0-6}alkyl$NR^4(CO)NR^4R^5$, $O(CO)NR^4R^5$, $NR^4(CO)OR^5$, C_{0-6}alkyl$(SO_2)NR^4R^5$, OC_{1-6}alkyl$(SO_2)NR^4R^5$, C_{0-6}alkyl$NR^4(SO_2)R^5$, OC_{1-6}alkyl$NR^4(SO_2)R^5$, C_{0-6}alkyl$(SO)NR^4R^5$, OC_{1-6}alkyl$(SO)NR^4R^5$, SO_3R^4, C_{1-6}alkyl$NR^4(SO_2)NR^4R^5$, C_{0-6}alkyl$NR^4(SO)R^5$, OC_{0-6}alkyl$NR^4(SO)R^5$, OC_{0-6}alkylSO_2R^4, C_{0-6}alkylSO_2R^4, C_{0-6}alkylSOR^4, OC_{1-6}alkylSOR^4 and a group R^6X^1,

wherein X^1 is a direct bond, O, $CONR^7R^8$, $SO_2NR^9R^{10}$, SO_2R^{11} or $NR^{12}R^{13}$;

R^7, R^9 and R^{12} each independently are hydrogen or C_{1-6}alkyl;

R^8, R^{10}, R^{11} and R^{13} are C_{0-4}alkyl;

R^6 is phenyl or a 5, 6 or 7-membered heterocyclic group containing one or two heteroatoms, selected independently from N, O and S, which heterocyclic group may be saturated or unsaturated or said phenyl or 5, 6 or 7-membered heterocyclic group may optionally be fused with a 5 or 6-membered saturated or unsaturated ring containing atoms selected independently from C, N, O and S and which phenyl or heterocyclic group may be substituted with one or two substituents selected from W;

R^6 is linked to R^8, R^{10}, R^{11} and R^{13};

n is 0, 1, 2, 3 or 4;

R^4 is independently selected from hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{0-6}alkylC_{3-6}cycloalkyl, C_{0-6}alkylaryl, C_{0-6}alkylheteroaryl, C_{1-6}alkyl$NR^{14}R^{15}$ and a 5 or 6 membered heterocyclic group containing one or two heteroatoms, selected independently from N, O and S, wherein said heterocyclic group may optionally be substituted by a group Y;

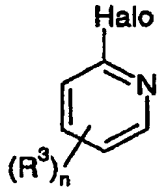
R^5 is independently selected from hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{0-6}alkylC_{3-6}cycloalkyl, C_{0-6}alkylaryl, C_{0-6}alkylheteroaryl and C_{1-6}alkyl$NR^{14}R^{15}$ and wherein R^4 and R^5 may together form a 4, 5, 6 or 7-membered heterocyclic group containing one or more heteroatoms selected independently from N, O and S, wherein said heterocyclic group may optionally be substituted by a group Y;

wherein any C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{0-6}alkylC_{3-6}cycloalkyl, C_{0-6}alkylaryl and C_{0-6}alkylheteroaryl defined under R^2 to R^5 may be substituted by one or more group Z;
R^{14} and R^{15} are independently selected from hydrogen, C_{1-6}alkyl and C_{0-6}alkylC_{3-6}cycloalkyl and wherein R^{14} and R^{15} may together form a 5 or 6-membered heterocyclic group containing one or more heteroatoms selected independently from N, O and S, wherein said heterocyclic group may optionally be substituted by a group Y;
W and Z are independently selected from oxo, halogen, nitro, CN, OR^{16}, C_{1-6}alkyl, C_{0-6}alkylaryl, C_{0-6}alkylC_{3-6}cycloalkyl, fluoromethyl, difluoromethyl, trifluoromethyl, fluoromethoxy, difluoromethoxy, trifluoromethoxy, OC_{1-6}alkyl$NR^{16}R^{17}$, $NR^{16}R^{17}$, $CONR^{16}R^{17}$, $NR^{16}(CO)R^{17}$, $O(CO)C_{1-6}$alkyl, $(CO)OC_{1-6}$alkyl, COR^{16}, $(SO_2)NR^{16}R^{17}$, SO_2R^{16}, SOR^{16}, $(CO)C_{1-6}$alkyl$NR^{16}R^{17}$, $(SO_2)C_{1-6}$alkyl$NR^{16}R^{17}$, phenyl and heteroaryl;
Y is selected from oxo, halogen, nitro, CN, OR^{16}, C_{1-6}alkyl, C_{0-6}alkylaryl, C_{0-6}alkylC_{3-6}cycloalkyl, fluoromethyl, difluoromethyl, trifluoromethyl, fluoromethoxy, difluoromethoxy, trifluoromethoxy, OC_{1-6}alkyl$NR^{16}R^{17}$, $NR^{16}R^{17}$, $CONR^{16}R^{17}$, $NR^{16}(CO)R^{17}$, $O(CO)C_{1-6}$alkyl, $(CO)OC_{1-6}$alkyl, COR^{16}, $(SO_2)NR^{16}R^{17}$, SO_2R^{16}, SOR^{16}, $(CO)C_{1-6}$alkyl$NR^{16}R^{17}$, $(SO_2)C_{1-6}$alkyl$NR^{16}R^{17}$, phenyl and heteroaryl, which phenyl or heteroaryl may optionally be substituted by a group W;
R^{16} and R^{17} are independently selected from hydrogen and C_{1-6}alkyl and wherein R^{16} and R^{17} may together form a 5 or 6-membered heterocyclic group containing one or more heteroatoms selected independently from N, O and S.

One aspect of the invention relates to compounds of formula **XXI**, wherein R^3 is selected from halogen, nitro, C_{1-6}alkyl, fluoromethyl, difluoromethyl, trifluoromethyl, fluoromethoxy, difluoromethoxy, trifluoromethoxy, OC_{1-6}alkylNR^4R^5, C_{0-6}alkylcyano, C_{0-6}alkyl$CONR^4R^5$, C_{0-6}alkyl$(SO_2)NR^4R^5$, C_{0-6}alkylNR^4R^5 and a group R^6X^1,
wherein X^1 is a direct bond, O, $CONR^7R^8$, $SO_2NR^9R^{10}$, SO_2R^{11} or $NR^{12}R^{13}$;
R^7, R^9 and R^{12} each independently are hydrogen or C_{1-3}alkyl;
R^8, R^{10}, R^{11} and R^{13} are C_{0-4}alkyl;
R^6 is phenyl or a 5, 6 or 7-membered heterocyclic group containing one or two heteroatoms, selected independently from N, O and S, which heterocyclic group may be saturated or unsaturated or said phenyl or 5, 6 or 7-membered heterocyclic group may optionally be fused with a 5 or 6-membered saturated or unsaturated ring containing atoms selected

independently from C, N, O and S and which phenyl or heterocyclic group may be subtituted with one or two substituents selected from W; and
R^6 is linked to R^8, R^{10}, R^{11} and R^{13}.

In a further aspect of the invention the intermediate is a compound of formula **XXII**



(XXII)

halo is halogen;
R^3 is selected from halogen, nitro, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{0-6}alkylC_{3-6}cycloalkyl, C_{0-6}alkylaryl, C_{0-6}alkylheteroaryl, CHO, C_{0-6}alkylOR^4, OC_{1-6}alkylOR^4, C_{1-6}alkylSR^4, OC_{1-6}alkylSR^4, $(CO)R^4$, $(CO)OR^4$, $O(CO)R^4$, fluoromethyl, difluoromethyl, trifluoromethyl, fluoromethoxy, difluoromethoxy, trifluoromethoxy, OC_{1-6}alkylcyano, C_{0-6}alkylcyano, C_{0-6}alkylCO_2R^4, OC_{1-6}alkylCO_2R^4, $O(CO)OR^4$, OC_{1-6}alkylCOR^4, C_{1-6}alkylCOR^4, NR^4OR^5, C_{0-6}alkylNR^4R^5, OC_{1-6}alkylNR^4R^5, C_{0-6}alkyl$CONR^4R^5$, OC_{1-6}alkyl$CONR^4R^5$, OC_{1-6}alkyl$NR^4(CO)R^5$, C_{0-6}alkyl$NR^4(CO)R^5$, C_{0-6}alkyl$NR^4(CO)NR^4R^5$, $O(CO)NR^4R^5$, $NR^4(CO)OR^5$, C_{0-6}alkyl$(SO_2)NR^4R^5$, OC_{1-6}alkyl$(SO_2)NR^4R^5$, C_{0-6}alkyl$NR^4(SO_2)R^5$, OC_{1-6}alkyl$NR^4(SO_2)R^5$, C_{0-6}alkyl$(SO)NR^4R^5$, OC_{1-6}alkyl$(SO)NR^4R^5$, SO_3R^4, C_{1-6}alkyl$NR^4(SO_2)NR^4R^5$, C_{0-6}alkyl$NR^4(SO)R^5$, OC_{0-6}alkyl$NR^4(SO)R^5$, OC_{0-6}alkylSO_2R^4, C_{0-6}alkylSO_2R^4, C_{0-6}alkylSOR^4, OC_{1-6}alkylSOR^4 and a group R^6X^1,
wherein X^1 is a direct bond, O, $CONR^7R^8$, $SO_2NR^9R^{10}$, SO_2R^{11} or $NR^{12}R^{13}$;
R^7, R^9 and R^{12} each independently are hydrogen or C_{1-6}alkyl;
R^8, R^{10}, R^{11} and R^{13} are C_{0-4}alkyl;
R^6 is phenyl or a 5, 6 or 7-membered heterocyclic group containing one or two heteroatoms, selected independently from N, O and S, which heterocyclic group may be saturated or unsaturated or said phenyl or 5, 6 or 7-membered heterocyclic group may optionally be fused with a 5 or 6-membered saturated or unsaturated ring containing atoms selected

independently from C, N, O and S and which phenyl or heterocyclic group may be substituted with one or two substituents selected from W;

R^6 is linked to R^8, R^{10}, R^{11} and R^{13};

n is 0, 1, 2, 3 or 4;

R^4 is independently selected from hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{0-6}alkylC_{3-6}cycloalkyl, C_{0-6}alkylaryl, C_{0-6}alkylheteroaryl, C_{1-6}alkyl$NR^{14}R^{15}$ and a 5 or 6 membered heterocyclic group containing one or two heteroatoms, selected independently from N, O and S, wherein said heterocyclic group may optionally be substituted by a group Y;

R^5 is independently selected from hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{0-6}alkylC_{3-6}cycloalkyl, C_{0-6}alkylaryl, C_{0-6}alkylheteroaryl and C_{1-6}alkyl$NR^{14}R^{15}$ and wherein R^4 and R^5 may together form a 4, 5, 6 or 7-membered heterocyclic group containing one or more heteroatoms selected independently from N, O and S, wherein said heterocyclic group may optionally be substituted by a group Y;

wherein any C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{0-6}alkylC_{3-6}cycloalkyl, C_{0-6}alkylaryl and C_{0-6}alkylheteroaryl defined under R^2 to R^5 may be substituted by one or more group Z;

R^{14} and R^{15} are independently selected from hydrogen, C_{1-6}alkyl and C_{0-6}alkylC_{3-6}cycloalkyl and wherein R^{14} and R^{15} may together form a 5 or 6-membered heterocyclic group containing one or more heteroatoms selected independently from N, O and S, wherein said heterocyclic group may optionally be substituted by a group Y;

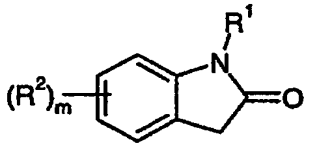
W and Z are independently selected from oxo, halogen, nitro, CN, OR^{16}, C_{1-6}alkyl, C_{0-6}alkylaryl, C_{0-6}alkylC_{3-6}cycloalkyl, fluoromethyl, difluoromethyl, trifluoromethyl, fluoromethoxy, difluoromethoxy, trifluoromethoxy, OC_{1-6}alkyl$NR^{16}R^{17}$, $NR^{16}R^{17}$, $CONR^{16}R^{17}$, $NR^{16}(CO)R^{17}$, $O(CO)C_{1-6}$alkyl, $(CO)OC_{1-6}$alkyl, COR^{16}, $(SO_2)NR^{16}R^{17}$, SO_2R^{16}, SOR^{16}, $(CO)C_{1-6}$alkyl$NR^{16}R^{17}$, $(SO_2)C_{1-6}$alkyl$NR^{16}R^{17}$, phenyl and heteroaryl;

Y is selected from oxo, halogen, nitro, CN, OR^{16}, C_{1-6}alkyl, C_{0-6}alkylaryl, C_{0-6}alkylC_{3-6}cycloalkyl, fluoromethyl, difluoromethyl, trifluoromethyl, fluoromethoxy, difluoromethoxy, trifluoromethoxy, OC_{1-6}alkyl$NR^{16}R^{17}$, $NR^{16}R^{17}$, $CONR^{16}R^{17}$, $NR^{16}(CO)R^{17}$, $O(CO)C_{1-6}$alkyl, $(CO)OC_{1-6}$alkyl, COR^{16}, $(SO_2)NR^{16}R^{17}$, SO_2R^{16}, SOR^{16}, $(CO)C_{1-6}$alkyl$NR^{16}R^{17}$, $(SO_2)C_{1-6}$alkyl$NR^{16}R^{17}$, phenyl and heteroaryl, which phenyl or heteroaryl may optionally be substituted by a group W;

R^{16} and R^{17} are independently selected from hydrogen and C_{1-6}alkyl and wherein R^{16} and R^{17} may together form a 5 or 6-membered heterocyclic group containing one or more heteroatoms selected independently from N, O and S.

One aspect of the invention relates to compounds of formula **XXII**, wherein R^3 is selected from halogen, nitro, C_{1-6}alkyl, fluoromethyl, difluoromethyl, trifluoromethyl, fluoromethoxy, difluoromethoxy, trifluoromethoxy, $OC_{1-6}alkylNR^4R^5$, C_{0-6}alkylcyano, $C_{0-6}alkylCONR^4R^5$, $C_{0-6}alkyl(SO_2)NR^4R^5$, $C_{0-6}alkylNR^4R^5$ and a group R^6X^1, wherein X^1 is a direct bond, O, $CONR^7R^8$, $SO_2NR^9R^{10}$, SO_2R^{11} or $NR^{12}R^{13}$;
R^7, R^9 and R^{12} each independently are hydrogen or C_{1-3}alkyl;
R^8, R^{10}, R^{11} and R^{13} are C_{0-4}alkyl;
R^6 is phenyl or a 5, 6 or 7-membered heterocyclic group containing one or two heteroatoms, selected independently from N, O and S, which heterocyclic group may be saturated or unsaturated or said phenyl or 5, 6 or 7-membered heterocyclic group may optionally be fused with a 5 or 6-membered saturated or unsaturated ring containing atoms selected independently from C, N, O and S and which phenyl or heterocyclic group may be subtituted with one or two substituents selected from W; and
R^6 is linked to R^8, R^{10}, R^{11} and R^{13}.

In yet another aspect of the invention the intermediate is a compound of formula **XXIII**



(XXIII)

wherein:
R^1 is hydrogen;
R^2 is selected from halogen, nitro, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, $C_{0-6}alkylC_{3-6}$cycloalkyl, C_{0-6}alkylaryl, C_{0-6}alkylheteroaryl, CHO, $C_{0-6}alkylOR^4$, $OC_{1-6}alkylOR^4$, $C_{1-6}alkylSR^4$, $OC_{1-6}alkylSR^4$, $(CO)R^4$, $(CO)OR^4$, $O(CO)R^4$, fluoromethyl, difluoromethyl, trifluoromethyl, fluoromethoxy, difluoromethoxy, trifluoromethoxy, OC_{1-6}alkylcyano, C_{0-6}alkylcyano, $C_{0-6}alkylCO_2R^4$, $OC_{1-6}alkylCO_2R^4$, $O(CO)OR^4$,

$OC_{1-6}alkylCOR^4$, $C_{1-6}alkylCOR^4$, NR^4OR^5, $C_{0-6}alkylNR^4R^5$, $OC_{1-6}alkylNR^4R^5$, $C_{0-6}alkylCONR^4R^5$, $OC_{1-6}alkylCONR^4R^5$, $OC_{1-6}alkylNR^4(CO)R^5$, $C_{0-6}alkylNR^4(CO)R^5$, $C_{0-6}alkylNR^4(CO)NR^4R^5$, $O(CO)NR^4R^5$, $NR^4(CO)OR^5$, $C_{0-6}alkyl(SO_2)NR^4R^5$, $OC_{1-6}alkyl(SO_2)NR^4R^5$, $C_{0-6}alkylNR^4(SO_2)R^5$, $OC_{1-6}alkylNR^4(SO_2)R^5$, $C_{0-6}alkyl(SO)NR^4R^5$, $OC_{1-6}alkyl(SO)NR^4R^5$, SO_3R^4, $C_{1-6}alkylNR^4(SO_2)NR^4R^5$, $C_{0-6}alkylNR^4(SO)R^5$, $OC_{0-6}alkylNR^4(SO)R^5$, $OC_{0-6}alkylSO_2R^4$, $C_{0-6}alkylSO_2R^4$, $C_{0-6}alkylSOR^4$, $OC_{1-6}alkylSOR^4$ and a group R^6X^1,

wherein X^1 is a direct bond, O, $CONR^7R^8$, $SO_2NR^9R^{10}$, SO_2R^{11} or $NR^{12}R^{13}$;

R^7, R^9 and R^{12} each independently are hydrogen or $C_{1-6}alkyl$;

R^8, R^{10}, R^{11} and R^{13} are $C_{0-4}alkyl$;

R^6 is phenyl or a 5, 6 or 7-membered heterocyclic group containing one or two heteroatoms, selected independently from N, O and S, which heterocyclic group may be saturated or unsaturated or said phenyl or 5, 6 or 7-membered heterocyclic group may optionally be fused with a 5 or 6-membered saturated or unsaturated ring containing atoms selected independently from C, N, O and S and which phenyl or heterocyclic group may be substituted with one or two substituents selected from W;

R^6 is linked to R^8, R^{10}, R^{11} and R^{13};

m is 0, 1, 2, 3 or 4;

R^4 is independently selected from hydrogen, $C_{1-6}alkyl$, $C_{2-6}alkenyl$, $C_{2-6}alkynyl$, $C_{0-6}alkylC_{3-6}cycloalkyl$, $C_{0-6}alkylaryl$, $C_{0-6}alkylheteroaryl$, $C_{1-6}alkylNR^{14}R^{15}$ and a 5 or 6 membered heterocyclic group containing one or two heteroatoms, selected independently from N, O and S, wherein said heterocyclic group may optionally be substituted by a group Y;

R^5 is independently selected from hydrogen, $C_{1-6}alkyl$, $C_{2-6}alkenyl$, $C_{2-6}alkynyl$, $C_{0-6}alkylC_{3-6}cycloalkyl$, $C_{0-6}alkylaryl$, $C_{0-6}alkylheteroaryl$ and $C_{1-6}alkylNR^{14}R^{15}$ and wherein R^4 and R^5 may together form a 4, 5, 6 or 7-membered heterocyclic group containing one or more heteroatoms selected independently from N, O and S, wherein said heterocyclic group may optionally be substituted by a group Y;

wherein any $C_{1-6}alkyl$, $C_{2-6}alkenyl$, $C_{2-6}alkynyl$, $C_{0-6}alkylC_{3-6}cycloalkyl$, $C_{0-6}alkylaryl$ and $C_{0-6}alkylheteroaryl$ defined under R^2 to R^5 may be substituted by one or more group Z;

R^{14} and R^{15} are independently selected from hydrogen, $C_{1-6}alkyl$ and

C_{0-6}alkylC_{3-6}cycloalkyl and wherein R^{14} and R^{15} may together form a 5 or 6-membered heterocyclic group containing one or more heteroatoms selected independently from N, O and S, wherein said heterocyclic group may optionally be substituted by a group Y;

W and Z are independently selected from oxo, halogen, nitro, CN, OR^{16}, C_{1-6}alkyl, C_{0-6}alkylaryl, C_{0-6}alkylC_{3-6}cycloalkyl, fluoromethyl, difluoromethyl, trifluoromethyl, fluoromethoxy, difluoromethoxy, trifluoromethoxy, OC_{1-6}alkyl$NR^{16}R^{17}$, $NR^{16}R^{17}$, $CONR^{16}R^{17}$, $NR^{16}(CO)R^{17}$, $O(CO)C_{1-6}$alkyl, $(CO)OC_{1-6}$alkyl, COR^{16}, $(SO_2)NR^{16}R^{17}$, SO_2R^{16}, SOR^{16}, $(CO)C_{1-6}$alkyl$NR^{16}R^{17}$, $(SO_2)C_{1-6}$alkyl$NR^{16}R^{17}$, phenyl and heteroaryl;

Y is selected from oxo, halogen, nitro, CN, OR^{16}, C_{1-6}alkyl, C_{0-6}alkylaryl, C_{0-6}alkylC_{3-6}cycloalkyl, fluoromethyl, difluoromethyl, trifluoromethyl, fluoromethoxy, difluoromethoxy, trifluoromethoxy, OC_{1-6}alkyl$NR^{16}R^{17}$, $NR^{16}R^{17}$, $CONR^{16}R^{17}$, $NR^{16}(CO)R^{17}$, $O(CO)C_{1-6}$alkyl, $(CO)OC_{1-6}$alkyl, COR^{16}, $(SO_2)NR^{16}R^{17}$, SO_2R^{16}, SOR^{16}, $(CO)C_{1-6}$alkyl$NR^{16}R^{17}$, $(SO_2)C_{1-6}$alkyl$NR^{16}R^{17}$, phenyl and heteroaryl, which phenyl or heteroaryl may optionally be substituted by a group W;

R^{16} and R^{17} are independently selected from hydrogen and C_{1-6}alkyl and wherein R^{16} and R^{17} may together form a 5 or 6-membered heterocyclic group containing one or more heteroatoms selected independently from N, O and S.

One aspect of the invention relates to compounds of formula **XXIII**, wherein R^2 is selected from halogen, nitro, C_{1-6}alkyl, fluoromethyl, difluoromethyl, trifluoromethyl, fluoromethoxy, difluoromethoxy, trifluoromethoxy, OC_{1-6}alkylNR^4R^5, C_{0-6}alkylcyano, C_{0-6}alkyl$CONR^4R^5$, C_{0-6}alkyl$(SO_2)NR^4R^5$, C_{0-6}alkylNR^4R^5 and a group R^6X^1,

wherein X^1 is a direct bond, O, $CONR^7R^8$, $SO_2NR^9R^{10}$, SO_2R^{11} or $NR^{12}R^{13}$;

R^7, R^9 and R^{12} each independently are hydrogen or C_{1-3}alkyl;

R^8, R^{10}, R^{11} and R^{13} are C_{0-4}alkyl;

R^6 is phenyl or a 5, 6 or 7-membered heterocyclic group containing one or two heteroatoms, selected independently from N, O and S, which heterocyclic group may be saturated or unsaturated or said phenyl or 5, 6 or 7-membered heterocyclic group may optionally be fused with a 5 or 6-membered saturated or unsaturated ring containing atoms selected independently from C, N, O and S and which phenyl or heterocyclic group may be subtituted with one or two substituents selected from W; and

R^6 is linked to R^8, R^{10}, R^{11} and R^{13}.

A further aspect of the invention relates to the following compounds, which may be used as intermediates in the preparation of a compound of formula I;
4-{2-[(6-Chloropyrimidine-4-yl)oxy]ethyl}morpholine,
1-[(6-Chloropyridine-3-yl)methyl]-4-methylpiperazine,
6-Chloropyridine-3-sulfonic acid (2-pyrrolidine-1-ylethyl)amide and
4-[(6-Chloro-1-oxidopyridine-3-yl)methyl]morpholine.

Working Examples

The invention will now be illustrated in the following non-limiting Examples and unless stated otherwise:
(i) temperatures are given in degrees Celsius (°C); operations were carried out at room temperature, i.e. at a temperature in the range of 18 to 25°C;
(ii) yields are given for illustration only and are not necessarily those which can be obtained by diligent process development; preparations were repeated if more material was required;
(iii) when given, NMR data is in the form of delta values, given in parts per million (ppm) relative to tetramethylsilane (TMS) as an internal standard, determined at 400 MHz using perdeuterio dimethyl sulphoxide (DMSO-d_6) or deuterio chloroform ($CDCl_3$) as solvent unless otherwise indicated;
(iv) chemical symbols have their usual meanings; SI units and symbols are used;
(v) solvent ratios are given in volume:volume (v/v) terms; and
(vi) mass spectra were run with an electron energy of 70 electron volts in the chemical ionization (CI) mode; where indicated ionization was effected by electron impact (EI), fast atom bombardment (FAB) or electrospray (ESP) unless otherwise indicated; values for m/z are given; generally, only ions which indicate the parent mass are reported.

Example 1

2-Chloro-*N*-[2-(dimethylamino)ethyl]-4-pyridinecarboxamide

To a solution of 2-chloroisonicotinic acid (0.50 g, 3.17 mmol) in *N,N*-dimethylformamide (20 mL) was added 1,1´-carbonyldiimidazole (0.565 g, 3.49 mmol). The solution was heated at 70 °C for 30 min. The reaction mixture was cooled to room temperature and

N,N-dimethylethylenediamine (0.31 g, 3.49 mmol) was added. The solution was stirred at room temperature overnight. The solvent was evaporated *in vacuo* and the residue was purified on a silica gel column using chloroform/methanol/conc. NH_3(aq), 90:10:1, as the eluent to afford 40 mg (57% yield) of the title compound as a colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.51 (d, *J*=5 Hz, 1 H), 7.68 (s, 1 H), 7.56 (dd, *J*=5, 1 Hz, 1 H), 6.92-7.08 (br s, 1 H), 3.58-3.48 (m, 2 H), 2.59-2.52 (m, 2 H), 2.28 (s 6 H); MS (TSP) *m/z* 228 (M^++1).

Example 2

2-(5-Cyano-2-hydroxy-1*H*-indol-3-yl)-*N*-[2-(dimethylamino)ethyl]-4-pyridinecarboxamide

To a suspension of sodium hydride (0.15 g, 3.70 mmol, 60% dispersion in oil, pre-washed with hexane) in *N,N*-dimethylformamide (3 mL) was added a solution of 5-cyanooxindole (0.29 g, 1.84 mmol) in *N,N*-dimethylformamide (4 mL). The mixture was stirred for 30 min under nitrogen atmosphere. 2-Chloro-*N*-[2-(dimethylamino)ethyl]-4-pyridinecarboxamide (0.21 g, 0.92 mmol) dissolved in *N,N*-dimethylformamide (4 mL) was added dropwise and the mixture was stirred at room temperature for 30 min and then heated at 150 °C for 45 min. The solvent was evaporated *in vacuo* and the residue was partitioned between ethyl acetate and water. A 2 M aqueous HCl solution was added until pH 2 and the mixture was extracted with ethyl acetate. To the aqueous layer a 45% aqueous NaOH solution was added until pH 11 and the suspension was extracted with ethyl acetate. The aqueous layer was concentrated *in vacuo* and the crude product was purified by preparative HPLC using a XTerracolumn (19x300 mm) with 0.05 M NH_4OAc buffert/ acetonitrile, 90:10-30:70 as a eluent as the eluent to give 15 mg (5% yield) of the title compound as a red solid: ^{1}H NMR (DMSO-d_6, 400 MHz) δ 15.01-14.75 (br s, 1 H), 11.10-10.97 (br s, 1 H), 9.11-9.09 (br s, 1 H), 8.28 (d, *J*=6 Hz, 1 H), 8.04-7.96 (m, 1 H), 7.95-7.83 (m, 1 H), 7.42-7.34 (m, 1 H), 7.13-7.02 (m, 2 H), 3.62-3.50 (m, 2 H), 2.86-2.69 (m, 2 H), 2.58-2.29 (m, 6 H); MS (TSP) *m/z* 350 (M^++1).

Example 3

1-[(2-Chloropyridine-4-yl)carbonyl]-4-methylpiperazine

The reaction was performed as described in Example 1 using 2-chloroisonicotinic acid (0.25 g, 1.75 mmol) and 1-methylpiperazine (0.19 mL, 1.92 mmol). The crude product was

purified on a silica gel column using chloroform/methanol/conc. NH_3(aq), 100:10:1, as the eluent to give 40 mg (57% yield) of the title compound as a colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.51 (d, *J*=5 Hz, 1 H), 7.57 (s, 1 H), 7.43 (dd, *J*=5, 1 Hz, 1 H), 3.66-3.58 (m, 2 H), 3.28-3.21 (m, 2 H), 2.41-2.34 (m, 2 H), 2.30-2.24 (m, 2 H), 2.20 (s, 3 H); MS (TSP) *m/z* 240 (M^++1).

Example 4

2-Hydroxy-3-[4-[(4-methylpiperazine-1-yl)carbonyl]pyridine-2-yl]-1*H*-indole-5-carbonitrile Dihydrochloride

The reaction was performed as described in Example 2 using 5-cyanooxindole (0.33 g, 2.08 mmol) and 1-[(2-chloropyridin-4-yl)carbonyl]-4-methylpiperazine (0.21 g, 0.92 mmol).

The crude product was purified on a silica gel column using chloroform/ethanol/ conc. NH_3(aq) 100:10:1, as the eluent. The base (20 mg) was dissolved in chloroform and a solution of HCl in diethyl ether was added until acidic pH. The formed precipitation was filtered and washed with diethyl ether. Drying *in vacuo* afforded 10 mg (2% yield) of the title compound as a red solid: ^{1}H NMR (D_2O, 400 MHz) δ 7.82-7.77 (m, 1 H), 7.18-7.11 (m, 1 H), 7.09-7.05 (m, 1 H), 7.04-6.98 (m, 1 H), 6.78-6.71 (m, 1 H), 6.67- 6.61 (m, 1 H), 4.05-3.94 (m, 1 H), 3.93-3.82 (m, 1 H), 3.67-3.48 (m, 2 H), 3.48-3.37 (m, 1 H), 3.35-3.04 (m, 3 H), 2.92-2.80 (m, 3 H); MS (TSP) *m/s* 362 (M^++1).

Example 5

4-{2-[(6-Chloropyrimidine-4-yl)oxy]ethyl}morpholine

To a solution of *N*-(2-hydroxyethyl)morpholine (1.09 g, 8.27 mmol) in *N,N*-dimethylformamide (5 mL) was added sodium hydride (364 mg, 9.10 mmol, 60% dispersion in oil) in portions. The mixture was stirred at room temperature for 1 h and at 45 °C for 1.5 h. The greenish solution was added dropwise over 5 min to a solution of 4,6-dichloropyrimidine (3.0 g, 20.1 mmol) in *N,N*-dimethylformamide (5 mL) and the reaction was continued for 30 min. The solvent was removed *in vacuo*, and the residue was partitioned between water and ethyl acetate. The organic layer was dried (Na_2SO_4) and the solvent was removed *in vacuo*. The crude product was purified on a silica gel column using ethyl acetate as the eluent affording 1.17 g (58% yield) of the title compound as a yellow

oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.57 (s, 1 H), 6.80 (s, 1 H), 4.53 (t, *J*=6 Hz, 2 H), 3.72 (t, *J*=5 Hz, 4 H), 2.77 (t, *J*=6 Hz, 2 H), 2.55 (t, *J*=4 Hz, 4 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.0, 160.7, 158.1, 108.0, 66.9, 64.6, 57.1, 53.9; MS (ESP) *m/z* 244 (M^++1).

Example 6

1-[(6-Chloropyridine-3-yl)methyl]-4-methylpiperazine

To a suspension of 2-chloro-5-chloromethylpyridine (971 mg, 5.99 mmol) in acetonitrile (50 mL) was added a solution of *N*-methylpiperazine (1.20 g, 12.0 mmol) in acetonitrile (3 mL) followed by potassium carbonate (0.83 g, 5.99 mmol). The obtained yellow solution was heated at reflux for 40 min. The mixture was allowed to cool for 10 min, and the solvent was removed *in vacuo*. The residue was partitioned between water, NaCl (s), and ethyl acetate. The aqueous layer was extracted with another portion of ethyl acetate. The combined organic layers were dried (Na_2SO_4) and the solvent was removed *in vacuo* affording 1.0 g (74% yield) of the title compound as a yellow oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.31 (d, *J*=2 Hz, 1 H), 7.65 (dd, *J*=8, 2 Hz, 1 H), 7.29 (d, *J*=8 Hz, 1 H), 3.49 (s, 2 H), 2.46 (br s, 8 H), 2.28 (s, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 150.2, 150.1, 139.5, 132.8, 124.0, 59.2, 55.0, 53.0, 46.0; MS (ESP) *m/z* 226 (M^++1).

Example 7

2-Hydroxy-3-{5-[(4-methylpiperazine-1-yl)carbonyl]pyridine-2-yl}-1*H*-indole-5-carbonitrile

A mixture of 5-cyanooxindole (213 mg, 1.35 mmol) and sodium hydride (72 mg, 1.80 mmol, 60% dispersion in oil) in *N,N*-dimethylformamide (4 mL) was stirred at room temperature for 10 min. A solution of 1-[(6-chloropyridin-3-yl)carbonyl]-4-methylpiperazine (216 mg, 0.901 mmol; described in: Thunus, L. *Ann. Pharm. Fr.* **1977**, *35(5-6)*, 197-203) in *N,N*-dimethylformamide (2 mL) was added dropwise. The reaction was stirred at room temperature for 3 h, then at 50 °C for 2.5 h. The solvent was removed *in vacuo*, and the residue was partitioned between chloroform and water. The pH was adjusted to 8 with a 2 M aqueous solution of HCl. The aqueous layer was extracted with ethyl acetate and the organic layers were dried (Na_2SO_4), combined, and the solvent was removed *in vacuo* affording an orange semi-solid. The material was purified on a silica gel column using chloroform/methanol, 80:20 as the eluent affording 24 mg (7% yield) of the

title compound as a yellow solid: mp decomposes >295 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.95 (s, 1 H), 7.91 (s, 1 H), 7.74 (dd, *J*=9, 2 Hz, 1 H), 7.69 (s, 1 H), 7.48 (d, *J*=9 Hz, 1 H), 7.36 (dd, *J*=8, 1 Hz, 1 H), 7.06 (d, *J*=8 Hz, 1 H), 3.69 (br s, 4 H); 2.48 (br s, 4 H), 2.36 (s, 3 H); MS (TSP) *m/z* 362 (M^++1).

Example 8

2-Hydroxy-3-[5-(morpholine-4-ylmethyl)pyridine-2-yl]-1*H*-indole-5-carbonitrile Hydrochloride

To a suspension of 5-cyanooxindole (720 mg, 4.55 mmol) in *N,N*-dimethylformamide (5 mL) was added sodium hydride (248 mg, 6.2 mmol, 60% dispersion in oil). To the obtained solution was added 4-[(6-chloropyridin-3-yl)methyl]morpholine (323 mg, 1.52 mmol; described in: Maienfisch, P. et al. *J. Med. Chem.* **2000**, *43*, 5003) after 15 min. The reaction mixture was heated at reflux for 1 h. The solvent was removed *in vacuo*, and the residue was partitioned between ethyl acetate and water. A 2 M aqueous HCl solution was added until slightly acidic pH, and then $NaHCO_3$ (s) was added until saturation. The mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried (Na_2SO_4) and the solvent was removed *in vacuo*. The crude product was dissolved in a mixture of methanol and ethyl acetate and was cooled on ice. A solution of HCl in diethyl ether was added until acidic pH. Approximately half of the solvent volume was removed *in vacuo*. The precipitated hydrochloride salt was filtered, washed with ethyl acetate, and dried *in vacuo*. The salt was converted back to the base by partitioning between ethyl acetate and a saturated $NaHCO_3$ solution. The obtained material (142 mg) was purified on a silica gel column using chloroform/ethanol, 90:10 as the eluent affording 34 mg (7% yield) of the title compound as a yellow solid: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 14.96 (br s, 1 H), 8.83 (br s, 1 H), 7.79 (dd, *J*=9, 1 Hz, 1 H), 7.69 (s, 1 H), 7.63 (s, 1 H), 7.50 (d, *J*=9 Hz, 1 H), 7.29-7.26 (m, 1 H), 7.06 (d, *J*=8 Hz, 1 H), 3.75-3.72 (m, 4 H), 3.44 (s, 2 H), 2.50-2.49 (m, 4 H).

The base was dissolved in a mixture of methanol, dichloromethane, and ethyl acetate (15 mL total volume) and was cooled on ice. A solution of HCl in diethyl ether was added until acidic pH. Approximately half of the solvent volume was removed *in vacuo*, and ethyl acetate was added. The precipitated hydrochloride salt was filtered, washed with ethyl acetate, and dried *in vacuo* at 40 °C affording 33 mg (87% yield from the base) as a yellow

solid: ^{1}H NMR (DMSO-*d6*, 400 MHz) δ 14.75 (br s, 1 H), 11.36 (br s, 1 H), 10.98 (s, 1 H), 8.30 (s, 1 H), 8.07-8.02 (m, 2 H), 7.90 (d, *J*=9 Hz, 1 H), 7.32 (d, *J*=8 Hz, 1 H), 7.02 (d, *J*=8 Hz, 1 H), 4.29 (s, 2 H), 3.98-3.94 (m, 2 H), 3.82-3.75 (m, 2 H), 3.37-3.32 (m, 2 H), 3.11-3.08 (m, 2 H); ^{13}C NMR (DMSO-*d6*, 100 MHz) δ 168.9, 148.4, 142.6, 139.7, 137.4, 124.8, 124.8, 120.8, 119.4, 118.4, 113.1, 108.9, 101.5, 85.6, 63.0, 55.5, 50.2; MS (TSP) m/z 335 (M^++1).

Example 9

2-Hydroxy-3-[6-(2-morpholine-4-ylethoxy)pyrimidine-4-yl]-1*H*-indole-5-carbonitrile

To a solution of 5-cyanooxindole (411 mg, 2.60 mmol) in *N,N*-dimethylformamide (4 mL) was added sodium hydride (181 mg, 4.52 mmol, 60% dispersion in oil). A solution of 4-{2-[(6-chloropyrimidin-4-yl)oxy]ethyl}morpholine (367 mg, 1.51 mmol) in *N,N*-dimethylformamide (1.5 mL) was added dropwise after 10 min. The mixture was stirred at room temperature for 3 h. The solvent was removed *in vacuo*, and the residue was suspended in a 2 M aqueous HCl solution and washed twice with ethyl acetate. The aqueous layer was alkalized to pH 8 by adding a 45% aqueous NaOH solution. The obtained suspension was extracted twice with ethyl acetate. The combined phases were washed with brine, dried (Na_2SO_4) and the solvent was removed *in vacuo*. The crude product was purified on a silica gel column using chloroform/ethanol, 90:10→chloroform/methanol, 80:20 as the eluent affording 172 mg (31% yield) of the title compound as a yellow solid: ^{1}H NMR (DMSO-*d6*, 400 MHz) δ 10.89 (br s, 1 H), 8.62 (s, 1 H), 8.02 (s, 1 H), 7.30 (d, *J*=7 Hz, 1 H), 6.97 (d, *J*=8 Hz, 1 H), 6.83 (br s, 1 H), 4.52 (t, *J*=5 Hz, 2 H), 3.60 (t, *J*=4 Hz, 4 H), 2.77 (m, 2 H), 2.54 (m, 4 H); MS (TSP) *m/z* 366 (M^++1).

Example 10

2-Hydroxy-3-{5-[(4-methylpiperazine-1-yl)methyl]pyridine-2-yl}-1*H*-indole-5-carbonitrile Hydrochloride

A mixture of 5-cyanooxindole (694 mg, 4.39 mmol) and sodium hydride (234 mg, 5.85 mmol, 60% dispersion in oil) in *N,N*-dimethylformamide (2.5 mL) was stirred at room temperature for 15 min. To the greenish solution was added a solution of 1-[(6-chloropyridin-3-yl)methyl]-4-methylpiperazine (330 mg, 1.46 mmol) in *N,N*-

dimethylformamide (1.2 mL) and the mixture was heated at 150 °C for 30 min. The mixture was allowed to cool and the solvent was removed *in vacuo*. The residue was suspended in a 2 M aqueous HCl solution and washed twice with ethyl acetate. The aqueous layer was alkalized with $NaHCO_3$ (s) until saturation followed by three extractions with ethyl acetate. The organic layers were combined, dried (Na_2SO_4), and the solvent was removed *in vacuo*. The obtained material was purified twice by column chromatography on silica using chloroform/methanol/conc. NH_3(aq) 90:10:0.5 as the eluent affording 56 mg of an oil. 38 mg of the oil was purified by preparative HPLC, using a XTerracolumn (19x300 mm) with 0.05 M NH_4OAc buffert/acetonitrile, 90:10-30:70 affording 29 mg (6% yield) of the title compound as a yellow solid: mp decomposes>240 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.74 (s, 1 H), 7.78 (d, *J*=9 Hz, 1 H), 7.70 (s, 1 H), 7.64 (s, 1 H), 7.50 (d, *J*=9 Hz, 1 H), 7.29 (m, 1 H), 7.06 (d, *J*=8 Hz, 1 H), 3.44 (s, 2 H), 2.52 (br s, 8 H), 2.31 (s, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 169.1, 149.6, 141.7, 136.1, 134.2, 125.4, 124.7, 123.6, 121.0, 119.7, 118.4, 109.3, 103.2, 85.4, 59.0, 55.0, 52.9, 45.9.

10 mg of the solid was dissolved in a mixture of ethyl acetate, dichloromethane, and a small volume of methanol (10 mL total volume). The solution was cooled on ice and HCl in diethyl ether was added until acidic pH. Approximately 2/3 of the solvent volume was removed *in vacuo* and ethyl acetate was added. The precipitated hydrochloride salt was filtered, washed with ethyl acetate and dried *in vacuo* affording 12 mg of the title compound as an orange solid: ^{1}H NMR (D_2O, 400 MHz) δ 7.78 (s, 1 H), 7.68-7.65 (m, 1 H), 7.47 (s, 1 H), 7.34-7.31 (m, 1 H), 7.14-7.11 (m, 1 H), 6.93-6.6.90 (m, 1 H), 3.62-3.48 (m, 10 H), 2.77 (s, 3 H); MS (TSP) *m/z* 348 (M^++1).

Example 11

2-Chloro-N-[2-(dimethylamino)ethyl]-*N*-methyl-3-pyridinecarboxamide

To a solution of *N,N*–dimethyl-N'-methylethylenediamine (1.0 g, 10 mmol) and triethylamine (2.0 g, 20 mmol) in methylene chloride (25 mL) was added 6-chloronicotinyl chloride (1.7 g, 10 mmol) in methylene chloride (50 mL) at room temperature. After 2 h at room temperature, the solvent was removed *in vacuo* and the residue was partitioned between a 2 M aqueous NaOH solution and methylene chloride (3x15 mL). The combined extracts were dried (Na_2SO_4) and the solvent was removed *in vacuo* to afford 2.6 g of a crude product. The residue was purified on a silica gel column using

acetonitril/triethylamine, 90:10 as the eluent to afford 2.1 g (87% yield) of the title compound as an bright yellow oil: ^{1}H NMR (DMSO-*d6*, 400 MHz) δ 8.62 (d, *J*=2 Hz, 1 H), 8.06 (dd, *J*=8, 2 Hz, 1 H), 7.76 (d, *J*=8 Hz, 1 H), 3.70 (s, 1 H), 3.41 (s, 1 H), 3.12 (d, *J*=19 Hz, 3 H), 2.64 (s, 1 H), 2.51 (s, 1 H), 2.37 (s, 3 H), 2.13 (s, 3 H); MS (TSP) *m/z* 242/244 (M^++1, 100/ 33).

Example 12

2-(5-Cyano-2-hydroxy-1*H*-indol-3-yl)-*N*-[2-(dimethylamino)ethyl]-*N*-methyl-3-pyridinecarboxamide Dihydrochloride

A mixture of sodium hydride (330 mg, 8.2 mmol, 60 % dispersion in oil, pre-washed with hexane) in *N,N*-dimethylformamide (2 mL) was added to 5-cyanooxindole (980 mg, 6.2 mmol) in *N,N*-dimethylformamide (4 mL). The formed brown mixture was stirred at room temperature for 20 min and 2-chloro-*N*-[2-(dimethylamino)ethyl]-*N*-methyl-3-pyridinecarboxamide (500 mg, 2.1 mmol) in *N,N*-dimethylformamide (3 mL) was added. The obtained red solution was heated at 150° C for 30 min and was then allowed to reach room temperature overnight. The solvent was removed *in vacuo* and the residue was partitioned between a 2 M aqueous HCl solution and ethyl acetate. The aqueous mixture was alkalized to pH 8 by adding $NaHCO_3$ (s) and extracted with ethyl acetate (3x10 mL). The combined extracts were dried (Na_2SO_4) and the solvent was removed *in vacuo* to afford 450 mg of a crude product. The residue was purified on a silica gel column using chloroform/ methanol/conc. NH_3(aq), 80:19:1, as the eluent. Fractions containing product were collected, evaporated *in vacuo* and dried at 25 °C *in vacuo* to afford 70 mg. The residue was purified by preparative HPLC using a XTerracolumn (19x300 mm) with 0.05 M NH_4OAc buffert/ acetonitrile, 90:10-30:70 as a eluent. Fractions containing product were collected and evaporated *in vacuo* and dried at 25 °C *in vacuo* to afford 35 mg (4.6% yield) of the title compound as a base: ^{1}H NMR (D_2O, 400 MHz) δ 7.89 (s, 1 H), 7.59 (d, *J*=9 Hz, 1 H), 6.96 (s, 1 H), 6.92 (d, *J*=8 Hz, 1 H), 6.84 (d, *J*=9 Hz, 1 H), 6.65 (d, *J*=8 Hz, 1 H), 3.76 (s, 2 H), 3.30 (s, 2 H), 3.07 (s, 3 H), 2.84 (s, 6 H).

10 mg of the residue was dissolved in diethyl ether and treated with 5 M HCl in diethyl ether. The dihydrochloride salt was dried at 25 °C *in vacuo* to afford 6 mg of the title compound as an orange powder: MS (ESP) *m/z* 364 (M^++1).

Example 13

2-Hydroxy-3-[5-(4-methylpiperazine-1-sulfonyl)pyridine-2-yl]-1*H*-indole-5-carbonitrile

The reaction was performed as described in Example 12 using 1-(6-chloro-pyridine-3-sulfonyl)-4-methylpiperazine (described in: Thunus L., Annales Pharmaceutiques Francaises **1977**, *35*, 197-204; (0.25 g, 0.9 mmol) to afford 36 mg (9.8% yield) of the title compound: ^{1}H NMR (D_2O, 400 MHz) δ 8.12 (s, 1 H), 7.60 (d, *J*=10 Hz, 1 H), 7.13 (s, 1 H), 7.00 (dd, *J*=8, 2 Hz, 1 H), 6.93 (d, *J*=9 Hz, 1 H), 6.73 (dd, *J*=8, 2 Hz, 1 H), 3.91 (d, *J*=13 Hz, 2 H), 3.60 (d, *J*=11 Hz, 2 H), 3.24 (app. t, *J*=11 Hz, 2 H), 3.02 (app. t, *J*=12 Hz, 2 H), 2.89 (s, 3 H); MS (TSP) *m/z* 398 (M^++1).

Example 14

6-Chloropyridine-3-sulfonic acid (2-pyrrolidine-1-ylethyl)amide

The reaction was performed as described in Example 11 using 2-pyrrolidin-1-yl-ethylamine (0.16 mL, 1.26 mmol). Purification on a silica gel column using ethyl acetate/triethylamine, 90:10 as the eluent gave 219 mg (58% yield) of the title compound: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.79 (d, *J*=2 Hz, 1 H), 8.05 (dd, *J*=8, 3 Hz, 1 H), 7.42 (d, *J*=9 Hz, 1 H), 3.00 (app. t, *J*=6 Hz, 2 H), 2.50 (app. t, *J*=6 Hz, 2 H), 2.33 (m, 4 H), 1.67 (m, 4 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 155.7, 148.8, 137.8, 136.1, 125.0, 54.1, 53.9, 41.6, 23.9; MS (TSP) *m/z* 290/ 292 (M^++1, 100/ 33).

Example 15

6-(5-Cyano-2-hydroxy-1*H*-indol-3-yl)pyridine-3-sulfonic acid (2-pyrrolidine-1-ylethyl)amide Dihydrochloride

The reaction was performed as described in Example 12 using 6-chloropyridine-3-sulfonic acid (2-pyrrolidin-1-ylethyl)amide (0.18 g, 0.62 mmol). Purification on a silica gel column using chloroform/methanol/conc. NH_3(aq), 80:19:1 as the eluent gave 36 mg (9.8% yield) of the title compound as the base. 15 mg of the residue was dissolved in methylene chloride/tetrahydrofuran/methanol (3 mL total volume) and treated with 5 M HCl in diethyl ether. The dihydrochloride salt was dried at 40 °C *in vacuo* to afford 11 mg of the title compound as an orange powder: ^{1}H NMR (D_2O, 400 MHz) δ 7.96 (s, 1 H), 7.47 (d, *J*=9 Hz, 1 H), 6.87 (s, 1 H), 6.74 (d, *J*=8 Hz, 1 H), 6.66 (d, *J*=9 Hz, 1 H), 6.50 (d, *J*= 8 Hz,

1 H), 3.61 (m, 2 H), 3.25 (m, 4 H), 3.02 (m, 2 H), 1.97 (m, 4 H); MS (TSP) *m/z* 412 (M^++1).

Example 16

2-Chloro-5-(chloromethyl)pyridine-1-oxide

To an ice-cooled suspension of 2-chloro-5-(chloromethyl)pyridine (1.61 g, 9.95 mmol) in chloroform (50 mL) was added *m*-chloroperoxybenzoic acid (3.72 g, 12.9 mmol) in portions. The ice-bath was removed and the mixture was allowed to reach room temperature. The solution was heated at 40 °C overnight. The solvent was removed *in vacuo* and the residual solid was purified on a silica gel column using ethyl acetate as the eluent affording 1.17 g (66% yield) of the title compound as a colorless solid: mp 89.5-89.7 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.41 (d, *J*=2 Hz, 1 H), 7.50 (d, *J*=8 Hz, 1 H), 7.25 (dd, *J*=8, 2 Hz, 1 H), 4.50 (s, 2 H); MS (ESP) *m/z* 178 (M^++1).

Example 17

4-[(6-Chloro-1-oxidopyridine-3-yl)methyl]morpholine

A mixture of 2-chloro-5-(chloromethyl)pyridine-1-oxide (1.16 g, 6.52 mmol), morpholine (1.14 g, 13.0 mmol), and potassium carbonate (0.90 g, 6.52 mmol) in acetonitrile (30 mL) was stirred at room temperature for 72 h. The solvent was removed *in vacuo* and the residue was purified on a silica gel column using chloroform/ethanol, 90:10 as the eluent affording 1.21 g (81% yield) of the title compound as a colorless solid: mp 72-74 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.34 (s, 1 H), 7.39 (d, *J*=8 Hz, 1 H), 7.16 (dd, *J*=8, *J*=2 Hz, 1 H), 3.65 (t, *J*=5 Hz, 4 H), 3.40 (s, 2 H), 2.40 (t, *J*=4 Hz, 4 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 140.4 (br), 135.9, 126.6, 126.6, 66.8, 59.2, 53.4; MS (ESP) *m/z* 229 (M^++1).

Example 18

2-Hydroxy-3-[5-(morpholine-4-ylmethyl)pyridine-2-yl]-1*H*-indole-5-carbonitrile

To a suspension of sodium hydride (105 mg, 2.62 mmol, 60% in oil) in *N,N*-dimethylformamide (2 mL) was added 5-cyanooxindole (310 mg, 1.96 mmol). The mixture was stirred at room temperature for 10 min. To the obtained yellowish solution was added 4-[(6-chloro-1-oxidopyridin-3-yl)methyl]morpholine (299 mg, 1.31 mmol) and the mixture was heated under nitrogen at 130 °C for 30 min. The dark reaction mixture was allowed to

cool and the solvent was removed *in vacuo*. The residue was partitioned between a 2 M aqueous solution of HCl and ethyl acetate. The aqueous layer was carefully saturated with $NaHCO_3$ (s) and extracted twice with ethyl acetate. The two last organic layers were combined, dried (Na_2SO_4) and the solvent was removed *in vacuo*. The residue was dissolved in ethyl acetate (50 mL) and a concentrated solution of phosphorus trichloride (0.5 mL, 5.7 mmol) in ethyl acetate (3 mL) was added. A yellowish precipitate was formed. The mixture was stirred at room temperature overnight and then heated at 60 °C for 30 min and finally at reflux for 10 min. The mixture was allowed to cool and was then diluted with ethyl actetate and washed with a saturated aqueous $NaHCO_3$ solution. The aqueous layer was extracted repeatedly with ethyl acetate. The combined organic layers were dried (Na_2SO_4) and the solvent was removed *in vacuo*. The residue was purified on a silica gel column using chloroform/ethyl acetate, 90:10 as the eluent affording 195 mg (45% yield) of the title compound as a yellow solid: mp 228-230 °C; ^{1}H NMR (DMSO, 400 MHz) δ 14.79 (br s, 1 H), 10.87 (s, 1 H), 8.10 (s, 1 H), 7.91 (s, 1 H), 7.84 (d, *J*=9 Hz, 1 H), 7.79 (dd, *J*=9, 1 Hz, 1 H), 7.28 (d, *J*=8 Hz, 1 H), 7.00 (d, *J*=8 Hz, 1 H), 3.58 (t, *J*=4 Hz, 4 H), 3.39 (s, 2 H), 2.38 (br s, 4 H); ^{13}C NMR (DMSO, 100 MHz) δ 168.6, 148.4, 142.0, 136.9, 135.9, 125.2, 124.0, 122.3, 121.0, 118.7, 118.3, 108.7, 101.2, 84.4, 66.1, 58.3, 52.8; MS (ESP) *m/z* 335 (M^++1).

Pharmacology

Determination of ATP competition in Scintillation Proximity GSK3β Assay.

GSK3β scintillation proximity assay.

The competition experiments were carried out in duplicate with 10 different concentrations of the inhibitors in clear-bottom microtiter plates (Wallac, Finland). A biotinylated peptide substrate, Biotin-Ala-Ala-Glu-Glu-Leu-Asp-Ser-Arg-Ala-Gly-Ser(PO_3H_2)-Pro-Gln-Leu (AstraZeneca, Lund), was added at a final concentration of 1 μM in an assay buffer containing 1 mU recombinant human GSK3β (Dundee University, UK), 12 mM morpholinepropanesulfonic acid (MOPS), pH 7.0, 0.3 mM EDTA, 0.01% β-mercaptorethanol, 0.004 % Brij 35 (a natural detergent), 0.5 % glycerol and 0.5 μg BSA/25

µl. The reaction was initiated by the addition of 0.04 µCi [γ-^{33}P]ATP (Amersham, UK) and unlabelled ATP at a final concentration of 1 µM and assay volume of 25 µl. After incubation for 20 minutes at room temperature, each reaction was terminated by the addition of 25 µl stop solution containing 5 mM EDTA, 50 µM ATP, 0.1 % Triton X-100 and 0.25 mg streptavidin coated Scintillation Proximity Assay (SPA) beads (Amersham, UK). After 6 hours the radioactivity was determined in a liquid scintillation counter (1450 MicroBeta Trilux, Wallac). The inhibition curves were analysed by non-linear regression using GraphPad Prism, USA. The K_m value of ATP for GSK3β, used to calculate the inhibition constants (K_i) of the various compounds, was 20 µM.

The following abbreviations have been used:

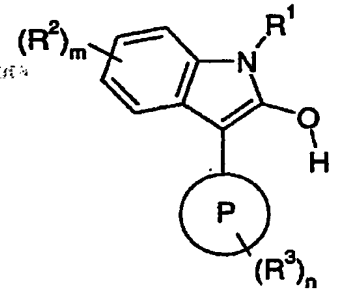
MOPS	Morpholinepropanesulfonic acid
EDTA	Ethylenediaminetetraacetic acid
BSA	Bovin Serum Albumin
ATP	Adenosine Triphophatase
SPA	Scintillation Proximity Assay
GSK3	Glycogen synthase kinase 3

Results

Typical K_i values for the compounds of the present invention are in the range of about 0.001 to about 10,000 nM. Other values for K_i are in the range of about 0.001 to about 1000 nM. Further values for K_i are in the range of about 0.010 nM to about 300 nM.

CLAIMS

1. A compound having the formula I



(I)

wherein:

P is a 5 or 6-membered heteroaromatic ring containing one or more heteroatoms selected independently from N, O and S of which at least one atom is selected from nitrogen;

R^1 is hydrogen;

R^2 and R^3 are independently selected from halogen, nitro, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{0-6}alkylC_{3-6}cycloalkyl, C_{0-6}alkylaryl, C_{0-6}alkylheteroaryl, CHO, C_{0-6}alkylOR^4, OC_{1-6}alkylOR^4, C_{1-6}alkylSR^4, OC_{1-6}alkylSR^4, $(CO)R^4$, $(CO)OR^4$, $O(CO)R^4$, fluoromethyl, difluoromethyl, trifluoromethyl, fluoromethoxy, difluoromethoxy, trifluoromethoxy, OC_{1-6}alkylcyano, C_{0-6}alkylcyano, C_{0-6}alkylCO_2R^4, OC_{1-6}alkylCO_2R^4, $O(CO)OR^4$, OC_{1-6}alkylCOR^4, C_{1-6}alkylCOR^4, NR^4OR^5, C_{0-6}alkylNR^4R^5, OC_{1-6}alkylNR^4R^5, C_{0-6}alkyl$CONR^4R^5$, OC_{1-6}alkyl$CONR^4R^5$, OC_{1-6}alkyl$NR^4(CO)R^5$, C_{0-6}alkyl$NR^4(CO)R^5$, C_{0-6}alkyl$NR^4(CO)NR^4R^5$, $O(CO)NR^4R^5$, $NR^4(CO)OR^5$, C_{0-6}alkyl$(SO_2)NR^4R^5$, OC_{1-6}alkyl$(SO_2)NR^4R^5$, C_{0-6}alkyl$NR^4(SO_2)R^5$, OC_{1-6}alkyl$NR^4(SO_2)R^5$, C_{0-6}alkyl$(SO)NR^4R^5$, OC_{1-6}alkyl$(SO)NR^4R^5$, SO_3R^4, C_{1-6}alkyl$NR^4(SO_2)NR^4R^5$, C_{0-6}alkyl$NR^4(SO)R^5$, OC_{0-6}alkyl$NR^4(SO)R^5$, OC_{0-6}alkylSO_2R^4, C_{0-6}alkylSO_2R^4, C_{0-6}alkylSOR^4, OC_{1-6}alkylSOR^4 and a group R^6X^1,

wherein X^1 is a direct bond, O, $CONR^7R^8$, $SO_2NR^9R^{10}$, SO_2R^{11} or $NR^{12}R^{13}$;

R^7, R^9 and R^{12} each independently are hydrogen or C_{1-6}alkyl;

R^8, R^{10}, R^{11} and R^{13} are C_{0-4}alkyl;

R^6 is phenyl or a 5, 6 or 7-membered heterocyclic group containing one or two heteroatoms, selected independently from N, O and S, which heterocyclic group may be saturated or unsaturated or said phenyl or 5, 6 or 7-membered heterocyclic group may optionally be fused with a 5 or 6-membered saturated or unsaturated ring containing atoms selected independently from C, N, O and S and which phenyl or heterocyclic group may be substituted with one or two substituents selected from W;

R^6 is linked to R^8, R^{10}, R^{11} and R^{13};

m is 0, 1, 2, 3 or 4;

n is 0, 1, 2, 3 or 4;

R^4 is independently selected from hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{0-6}alkylC_{3-6}cycloalkyl, C_{0-6}alkylaryl, C_{0-6}alkylheteroaryl, C_{1-6}alkyl$NR^{14}R^{15}$ and a 5 or 6 membered heterocyclic group containing one or two heteroatoms, selected independently from N, O and S, wherein said heterocyclic group may optionally be substituted by a group Y;

R^5 is independently selected from hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{0-6}alkylC_{3-6}cycloalkyl, C_{0-6}alkylaryl, C_{0-6}alkylheteroaryl and C_{1-6}alkyl$NR^{14}R^{15}$ and wherein R^4 and R^5 may together form a 4, 5, 6 or 7-membered heterocyclic group containing one or more heteroatoms selected independently from N, O and S, wherein said heterocyclic group may optionally be substituted by a group Y;

wherein any C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{0-6}alkylC_{3-6}cycloalkyl, C_{0-6}alkylaryl and C_{0-6}alkylheteroaryl defined under R^2 to R^5 may be substituted by one or more group Z;

R^{14} and R^{15} are independently selected from hydrogen, C_{1-6}alkyl and C_{0-6}alkylC_{3-6}cycloalkyl and wherein R^{14} and R^{15} may together form a 5 or 6-membered heterocyclic group containing one or more heteroatoms selected independently from N, O and S, wherein said heterocyclic group may optionally be substituted by a group Y;

W and Z are independently selected from oxo, halogen, nitro, CN, OR^{16}, C_{1-6}alkyl, C_{0-6}alkylaryl, C_{0-6}alkylC_{3-6}cycloalkyl, fluoromethyl, difluoromethyl, trifluoromethyl, fluoromethoxy, difluoromethoxy, trifluoromethoxy, OC_{1-6}alkyl$NR^{16}R^{17}$, $NR^{16}R^{17}$, $CONR^{16}R^{17}$, $NR^{16}(CO)R^{17}$, $O(CO)C_{1-6}$alkyl, $(CO)OC_{1-6}$alkyl, COR^{16}, $(SO_2)NR^{16}R^{17}$, SO_2R^{16}, SOR^{16}, $(CO)C_{1-6}$alkyl$NR^{16}R^{17}$, $(SO_2)C_{1-6}$alkyl$NR^{16}R^{17}$, phenyl and heteroaryl;

Y is selected from oxo, halogen, nitro, CN, OR^{16}, C_{1-6}alkyl, C_{0-6}alkylaryl,

C_{0-6}alkylC_{3-6}cycloalkyl, fluoromethyl, difluoromethyl, trifluoromethyl, fluoromethoxy, difluoromethoxy, trifluoromethoxy, OC_{1-6}alkyl$NR^{16}R^{17}$, $NR^{16}R^{17}$, $CONR^{16}R^{17}$, $NR^{16}(CO)R^{17}$, $O(CO)C_{1-6}$alkyl, $(CO)OC_{1-6}$alkyl, COR^{16}, $(SO_2)NR^{16}R^{17}$, SO_2R^{16}, SOR^{16}, $(CO)C_{1-6}$alkyl$NR^{16}R^{17}$, $(SO_2)C_{1-6}$alkyl$NR^{16}R^{17}$, phenyl and heteroaryl, which phenyl or heteroaryl may optionally be substituted by a group W;

R^{16} and R^{17} are independently selected from hydrogen and C_{1-6}alkyl and wherein R^{16} and R^{17} may together form a 5 or 6-membered heterocyclic group containing one or more heteroatoms selected independently from N, O and S;

as a free base or a pharmaceutically acceptable salt thereof.

2. The compound according to claim 1, wherein ring P is a 6-membered heteroaromatic ring containing one or two nitrogen atoms.

3. The compound according to claim 1, wherein ring P is pyridine.

4. The compound according to claim 1, wherein ring P is pyrimidine.

5. The compound according to any one of claims 1 to 4, wherein R^2 and R^3 are independently selected from halogen, nitro, C_{1-6}alkyl, fluoromethyl, difluoromethyl, trifluoromethyl, fluoromethoxy, difluoromethoxy, trifluoromethoxy, OC_{1-6}alkylNR^4R^5, C_{0-6}alkylcyano, C_{0-6}alkyl$CONR^4R^5$, C_{0-6}alkyl$(SO_2)NR^4R^5$, C_{0-6}alkylNR^4R^5 and a group R^6X^1,

wherein X^1 is a direct bond, O, $CONR^7R^8$, $SO_2NR^9R^{10}$, SO_2R^{11} or $NR^{12}R^{13}$;

R^7, R^9 and R^{12} each independently are hydrogen or C_{1-3}alkyl;

R^8, R^{10}, R^{11} and R^{13} are C_{0-4}alkyl;

R^6 is phenyl or a 5, 6 or 7-membered heterocyclic group containing one or two heteroatoms, selected independently from N, O and S, which heterocyclic group may be saturated or unsaturated or said phenyl or 5, 6 or 7-membered heterocyclic group may optionally be fused with a 5 or 6-membered saturated or unsaturated ring containing atoms selected independently from C, N, O and S and which phenyl or heterocyclic group may be subtituted with one or two substituents selected from W; and

R^6 is linked to R^8, R^{10}, R^{11} and R^{13}.

6. The compound according to any one of claims 1 to 4, wherein R^2 and R^3 are independently selected from nitro, C_{1-3}alkyl, C_{0-3}alkylcyano, C_{0-3}alkylNR^4R^5, OC_{1-3}alkylNR^4R^5, C_{0-3}alkyl$CONR^4R^5$ and C_{0-3}alkyl$(SO_2)NR^4R^5$.

7. The compound according to any of claims 1 to 6, wherein R^4 is independently selected from hydrogen, C_{1-6}alkyl and a 5 or 6 membered heterocyclic group containing one or two heteroatoms, selected independently from N, O and S, wherein said heterocyclic group may optionally be substituted by a group Y;

R^5 is independently selected from hydrogen, C_{1-6}alkyl and C_{1-6}alkyl$NR^{14}R^{15}$ and wherein R^4 and R^5 may together form a 4, 5, 6 or 7-membered heterocyclic group containing one or more heteroatoms selected independently from N and O, wherein said heterocyclic group may optionally be substituted by a group Y;

R^{14} and R^{15} are independently selected from hydrogen and C_{1-6}alkyl and wherein R^{14} and R^{15} may together form a 5 or 6-membered heterocyclic group containing one or more heteroatoms selected independently from N and O, wherein said heterocyclic group may optionally be substituted by a group Y.

8. A compound which is

2-(5-Cyano-2-hydroxy-1*H*-indol-3-yl)-*N*-[2-(dimethylamino)ethyl]-4-pyridinecarboxamide,

2-Hydroxy-3-[4-[(4-methylpiperazine-1-yl)carbonyl]pyridine-2-yl]-1*H*-indole-5-carbonitrile dihydrochloride,

2-Hydroxy-3-{5-[(4-methylpiperazine-1-yl)carbonyl]pyridine-2-yl}-1*H*-indole-5-carbonitrile,

2-Hydroxy-3-[5-(morpholine-4-ylmethyl)pyridine-2-yl]-1*H*-indole-5-carbonitrile hydrochloride,

2-Hydroxy-3-[6-(2-morpholine-4-ylethoxy)pyrimidine-4-yl]-1*H*-indole-5-carbonitrile,

2-Hydroxy-3-{5-[(4-methylpiperazine-1-yl)methyl]pyridine-2-yl}-1*H*-indole-5-carbonitrile hydrochloride,

2-(5-Cyano-2-hydroxy-1*H*-indol-3-yl)-*N*-[2-(dimethylamino)ethyl]-*N*-methyl-3-pyridinecarboxamide dihydrochloride,

2-Hydroxy-3-[5-(4-methylpiperazine-1-sulfonyl)pyridine-2-yl]-1*H*-indole-5-carbonitrile and

6-(5-Cyano-2-hydroxy-1*H*-indol-3-yl)pyridine-3-sulfonic acid (2-pyrrolidine-1-ylethyl)amide dihydrochloride,

as a free base or a pharmaceutically acceptable salt thereof.

9. A pharmaceutical formulation comprising as active ingredient a therapeutically effective amount of the compound of any one of claims 1 to 8 in association with pharmaceutically acceptable carriers or diluents.

10. The pharmaceutical formulation according to claim 9 for use in the prevention and/or treatment of conditions associated with glycogen synthase kinase-3.

11. The pharmaceutical formulation according to any one of claims 9 and 10 for use in the prevention and/or treatment of one or more conditions such as dementia, Alzheimer's Disease, Parkinson's Disease, Frontotemporal dementia Parkinson's Type, Parkinson dementia complex of Gaum, HIV dementia, diseases with associated neurofibrillar tangle pathologies, amyotrophic lateral sclerosis, corticobasal degeneration, dementia pugilistica, Down's syndrome, Huntington's Disease, postencephelatic parkinsonism, progressive supranuclear palsy, Pick's Disease Niemann-Pick's Disease, stroke, head trauma and other chronic neurodegenerative diseases, Bipolar Disease, affective disorders, depression, schizophrenia, cognitive disorders, Type I and Type II diabetes, diabetic neuropathy, hair loss and contraceptive medication.

12. The pharmaceutical formulation according to claim 11, wherein the condition is dementia and Alzheimer's Disease.

13. The compound as defined in any one of claims 1 to 8 for use in therapy.

14. Use of a compound defined in any one of claims 1 to 8 in the manufacture of a medicament for the prevention and/or treatment of conditions associated with glycogen synthase kinase-3.

15. The use according to claim 14 in the manufacture of a medicament for the prevention and/or treatment of one or more conditions such as dementia, Alzheimer's Disease, Parkinson's Disease, Frontotemporal dementia Parkinson's Type, Parkinson dementia complex of Gaum, HIV dementia, diseases with associated neurofibrillar tangle pathologies, amyotrophic lateral sclerosis, corticobasal degeneration, dementia pugilistica, Down's syndrome, Huntington's Disease, postencephelatic parkinsonism, progressive supranuclear palsy, Pick's Disease, Niemann-Pick's Disease, stroke, head trauma and other chronic neurodegenative diseases, Bipolar Disease, affective disorders, depression, schizophrenia, cognitive disorders, Type I and Type II diabetes, diabetic neuropathy, hair loss and contraceptive medication.

16. The use according to claim 15, wherein the condition is dementia and Alzheimer's Disease.

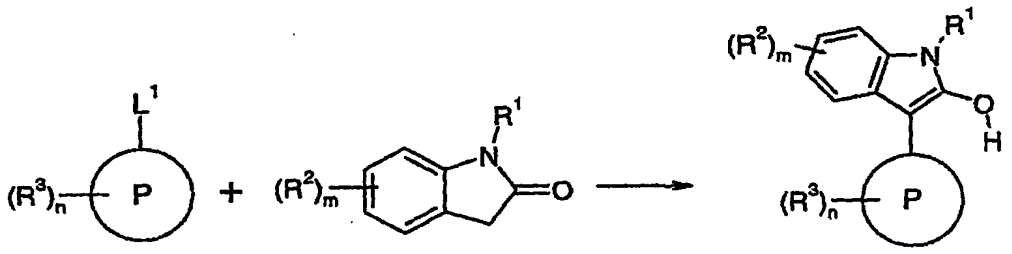
17. A method of prevention and/or treatment of conditions associated with glycogen synthase kinase-3, comprising administering to a mammal, including man in need of such prevention and/or treatment, a therapeutically effective amount of a compound of formula I as defined in any one of claims 1 to 8.

18. The method according to claim 17, wherein the condition is one or more of dementia, Alzheimer's Disease, Parkinson's Disease, Frontotemporal dementia Parkinson's Type, Parkinson dementia complex of Gaum, HIV dementia, diseases with associated neurofibrillar tangle pathologies, amyotrophic lateral sclerosis, corticobasal degeneration, dementia pugilistica, Down's syndrome, Huntington's Disease, postencephelatic parkinsonism, progressive supranuclear palsy, Niemann-Pick's Disease, Pick's Disease, stroke, head trauma and other chronic neurodegenative diseases, Bipolar Disease, affective disorders, depression, schizophrenia, cognitive disorders, Type I and Type II diabetes, diabetic neuropathy, hair loss and contraceptive medication.

19. The method according to claim 18, wherein the condition is dementia and Alzheimer's Disease.

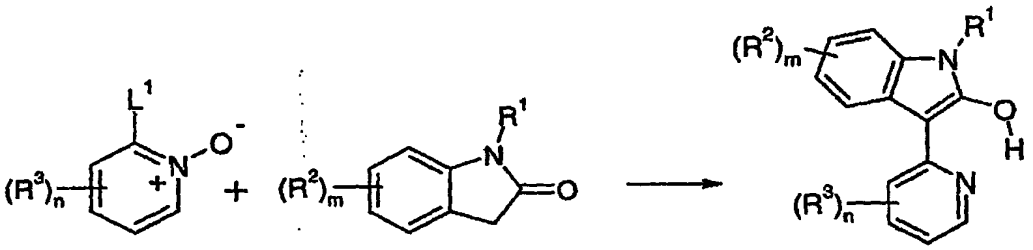
20. A process for the preparation of a compound of formula **I** according to claim 1, comprising:

a) reacting a compound of formula **B**, wherein L^1 is a leaving group such as halogen, e.g. fluorine, chlorine or bromine, with a compound of formula **C**,



(B (XII, XIV, XVI, XVIII)) **(C (III, V, VII, IX, X))** **(I)**

b) reacting a compound of formula **D**, wherein L^1 is a leaving group such as halogen, e.g. fluorine, chlorine or bromine, with a compound of formula **C**, followed by the removal of the *N*-oxide, to form a compound of formula **I**, wherein P is a pyridine,



(D (XX)) **(C (III, V, VII, IX, X))** **(I)**

21. A compound which is

4-{2-[(6-Chloropyrimidine-4-yl)oxy]ethyl}morpholine,

1-[(6-Chloropyridine-3-yl)methyl]-4-methylpiperazine,

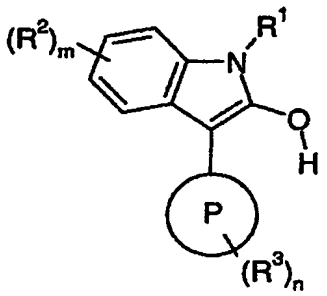
6-Chloropyridine-3-sulfonic acid (2-pyrrolidine-1-ylethyl)amide or

4-[(6-Chloro-1-oxidopyridine-3-yl)methyl]morpholine.

22. The use of the compounds according to claim 21 in the preparation of a compound of formula I as defined in any one of claims 1 to 8.

ABSTRACT

The present invention relates to new compounds of formula I,



as well as a process for their preparation and new intermediates used therein, pharmaceutical formulations containing said therapeutically active compounds and to the use of said active compounds in therapy.